

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



In re application of:

BUSH *et al.*

Appl. No. 09/972,913

Filed: October 10, 2001

For: Use of Clioquinol for the Therapy
of Alzheimer's Disease

Confirmation No. 5681

Art Unit: 1615

Examiner: *To be assigned*

Atty. Docket: 0609.4540003/JAG/FRC

**Petition to Revive Abandoned Application
Under 37 C.F.R. § 1.137(b)**

Commissioner for Patents
Washington, DC 20231

Box: DAC

Sir:

Applicants submit this petition under 37 C.F.R. § 1.137(b) to revive the above-captioned application. Accompanying this petition are the following:

1. Petition fee as set forth in 37 C.F.R. § 1.17(m);
2. Copies of the following documents that were submitted to the USPTO on **September 11, 2002** in reply to the outstanding Decision Refusing Status Under 37 C.F.R. § 1.47(a):
 - (i) Request for Reconsideration of Petition Under 37 C.F.R. § 1.47(a);
 - (ii) Affidavit in Support of Request for Reconsideration of Petition Under 37 C.F.R. § 1.47(a) along with Exhibits A-I;
 - (iii) Petition for Extension of Time Under 37 C.F.R. § 1.136(a)(1);
 - (iv) SKGF Cover Letter;
 - (v) Fee Transmittal Form (PTO/SB/17); and

Repln. Ref: 03/10/2003 AKELLEY 0008460200
DAM: 190036 Name/Number: 09972913 (vi)
FC: 9204 \$640.00 CR

Our check no. 36617 in the amount of \$980.00 to cover the extension of time fee (5 months); and

3. Copy of the date-stamped return postcard indicating receipt of the above-listed items by the USPTO on September 11, 2002.

09/25/2002 MBLANCO 00000012 09972913

01 FC:241 640.00 OP
Adjustment date: 03/10/2003 AKELLEY
09/25/2002 MBLANCO 00000012 09972913
01 FC:241 -640.00 OP

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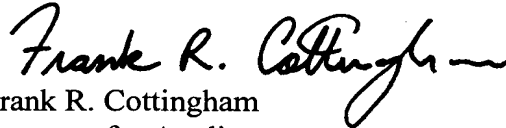
SEP 26 2002

OFFICE OF PETITIONS

The entire delay in providing the required reply from the due date for the reply until the filing of this grantable petition pursuant to this paragraph was unintentional.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Frank R. Cottingham
Attorney for Applicants
Registration No. 50,437

Date: 7/24/02

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600

DAC



Robert Greene Sterne
Edward J. Kessler
Jorge A. Goldstein
David K.S. Cornwell
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Tracy-Gene G. Durkin
Michele A. Cimbala
Michael B. Ray
Robert E. Sokohl
Eric K. Steffe
Michael Q. Lee
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W. Russell Swindell

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Virgil Lee Beaton
Reginald D. Lucas
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Elizabeth J. Haanes
Bruce E. Chalkoff
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Frank R. Cottingham
Christine M. Lhulier
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Jane Shershenovich
Lawrence J. Carroll
George S. Bardmesser
Daniel A. Klien
Rodney G. Maze
Jason D. Eisenberg
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Registered Patent Agents*
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Matthew J. Dowd
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Katrina Y. Pei
Bryan L. Skelton
Robert A. Schwartzman
John J. Figueroa
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Jennifer R. Mahalingappa

Senior Counsel
Samuel L. Fox
Kenneth C. Bass III
Lisa A. Dunner

*Admitted only in Maryland
*Admitted only in Virginia
*Admitted only in Texas
*Practice Limited to Federal Agencies

September 24, 2002

WRITER'S DIRECT NUMBER:
(202) 371-2615
INTERNET ADDRESS:
FRANKC@SKGF.COM

Commissioner for Patents
Washington, D.C. 20231

Box DAC

Re: U.S. Utility Patent Application
Appl. No. 09/972,913; Filed: October 10, 2001
For: Use of Clioquinol for the Therapy of Alzheimer's Disease
Inventors: BUSH *et al.*
Our Ref: 0609.4540003/JAG/FRC

RECEIVED

SEP 26 2002

OFFICE OF PETITIONS

Sir:

Transmitted herewith for appropriate action are the following documents:

1. Copy of Notice of Abandonment Under 37 C.F.R. 1.53 (f) or (g);
2. Request to Withdraw Abandonment along with copies of the following enclosures:
 - i. Request for Reconsideration of Petition Under 37 C.F.R. §1.47(a);
 - ii. Affidavit in Support of Request for Reconsideration of Petition Under 37 C.F.R. § 1.47(a) along with Exhibits A-I;
 - iii. Petition for Extension of Time Under 37 C.F.R. § 1.136(a)(1);
 - iv. SKGF Cover Letter;
 - v. Fee Transmittal Form (PTO/SB/17); and
 - vi. Our check no. **36617** in the amount of **\$980.00** to cover the extension of time fee (5 months);
3. Copy of the date-stamped return postcard indicating receipt of the above-listed items (i-vi) on September 11, 2002; and
4. One (1) return postcard.

Commissioner for Patents
September 24, 2002
Page 2

It is respectfully requested that the attached postcard be stamped with the date of filing of these documents, and that it be returned to our courier. In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Frank R. Cottingham
Attorney for Applicants
Registration No. 50,437

JAG/FRC/shr
Enclosures

::ODMA\HODMA\SKGF_DC1;57862;1



Robert Greene Sterne
Edward J. Kessler
Jorge A. Goldstein
David K.S. Cornwell
Robert W. Esmond
Tracy-Gene G. Durkin
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September 24, 2002

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Commissioner for Patents
Washington, D.C. 20231

Box DAC

Re: U.S. Utility Patent Application
Appl. No. 09/972,913; Filed: October 10, 2001
For: Use of Clotiquinol for the Therapy of Alzheimer's Disease
Inventors: Bush *et al.*
Our Ref: 0609.4540003/JAG/FRC

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OFFICE OF PETITIONS

Sir:

Transmitted herewith for appropriate action are the following documents:

1. Copy of Notice of Abandonment Under 37 C.F.R. § 1.53 (f) or (g);
2. Fee Transmittal Form (PTO/SB/17);
3. Petition to Revive Abandoned Application Under 37 C.F.R. § 1.137(b) along with copies of the following enclosures:
 - i. Request for Reconsideration of Petition Under 37 C.F.R. § 1.47(a);
 - ii. Affidavit in Support of Request for Reconsideration of Petition Under 37 C.F.R. § 1.47(a) along with Exhibits A-I;
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September 24, 2002
Page 2

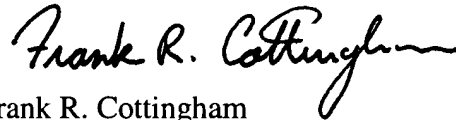
5. Our check no. **36747** in the amount of **\$640.00** to cover the Petition to Revive Abandoned Application fee; and
6. One (1) return postcard.

It is respectfully requested that the attached postcard be stamped with the date of filing of these documents, and that it be returned to our courier. In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

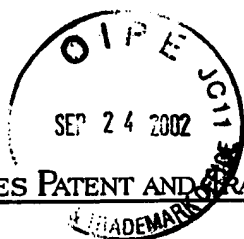
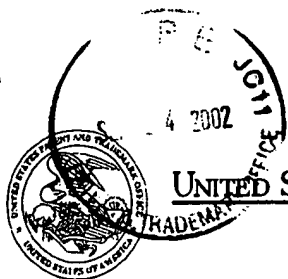
STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Frank R. Cottingham
Attorney for Applicants
Registration No. 50,437

JAG/FRC/shr
Enclosures

::ODMA\HODMA\SKGF_DC1;58028;1



UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO. TITLE
09/972,913	10/10/2001	Ashley I. Bush	0609.4540003

26111
STERNE, KESSLER, GOLDSTEIN & FOX PLLC
1100 NEW YORK AVENUE, N.W., SUITE 600
WASHINGTON, DC 20005-3934

CONFIRMATION NO. 5681

ABANDONMENT/TERMINATION
LETTER

OC000000008791936

Date Mailed: 09/16/2002

NOTICE OF ABANDONMENT UNDER 37 CFR 1.53 (f) OR (g)

The above-identified application is abandoned for failure to timely or properly reply to the Notice to File Missing Parts (Notice) mailed on 02/11/2002.

- No reply was received.

A petition to the Commissioner under 37 CFR 1.137 may be filed requesting that the application be revived.

Under 37 CFR 1.137(a), a petition requesting the application be revived on the grounds of **UNAVOIDABLE DELAY** must be filed promptly after the applicant becomes aware of the abandonment and such petition must be accompanied by: (1) an adequate showing of the cause of unavoidable delay; (2) the required reply to the above-identified Notice; (3) the petition fee set forth in 37 CFR 1.17(l); and (4) a terminal disclaimer if required by 37 CFR 1.137(d).

Under 37 CFR 1.137(b), a petition requesting the application be revived on the grounds of **UNINTENTIONAL DELAY** must be filed promptly after applicant becomes aware of the abandonment and such petition must be accompanied by: (1) a statement that the entire delay was unintentional; (2) the required reply to the above-identified Notice; (3) the petition fee set forth in 37 CFR 1.17(m); and (4) a terminal disclaimer if required by 37 CFR 1.137(d).

Any questions concerning petitions to revive should be directed to "Office of Petitions" at (703) 305-9282.

*A copy of this notice **MUST** be returned with the reply.*

Customer Service Center

Initial Patent Examination Division (703) 308-1202

PART 2 - COPY TO BE RETURNED WITH RESPONSE

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OFFICE OF PETITIONS



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

BUSH *et al.*

Appl. No. 09/972,913

Filed: October 10, 2001

For: **Use of Clioquinol for the Therapy
of Alzheimer's Disease**

Confirmation No. 5681

Art Unit: 1615

Examiner: *To be assigned*

Atty. Docket: 0609.4540003/JAG/FRC

Request to Withdraw Abandonment

Commissioner for Patents
Washington, DC 20231

Sir:

A Notice of Abandonment was mailed on September 16, 2002, for the above-captioned application. The Notice indicates that the application is abandoned in view of Applicants' failure to timely or properly reply to the Notice to File Missing Parts mailed on February 11, 2002.

Applicants respectfully note that a Notice to File Missing Parts, dated February 11, 2002, was never received by the undersigned. However, a "Decision Refusing Status Under 37 C.F.R. § 1.47(a)," dated February 11, 2002, was received. In reply to the Decision Refusing Status Under 37 C.F.R. § 1.47(a), Applicants timely submitted the following items on **September 11, 2002**:

- (1) Request for Reconsideration of Petition Under 37 C.F.R. § 1.47(a);
- (2) Affidavit in Support of Request for Reconsideration of Petition Under 37 C.F.R. § 1.47(a) along with Exhibits A-I;
- (3) Petition for Extension of Time Under 37 C.F.R. § 1.136(a)(1);
- (4) SKGF Cover Letter;
- (5) Fee Transmittal Form (PTO/SB/17); and
- (6) Our check no. **36617** in the amount of **\$980.00** to cover the extension of time fee (5 months).

Enclosed herewith are copies of the above-listed items. Also enclosed is a copy of the date-stamped return postcard indicating receipt of the above-listed items by the U.S. Patent and Trademark Office on September 11, 2002.

RECEIVED

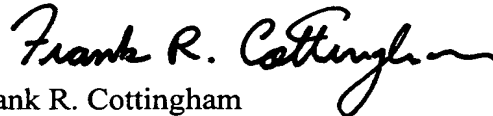
SEP 26 2002

OFFICE OF PETITIONS

Accordingly, it is respectfully submitted that the Notice of Abandonment is in error.
Early notification of withdrawal of the abandonment is earnestly solicited.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Frank R. Cottingham
Attorney for Applicants
Registration No. 50,437

Date: 9/24/02

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600

FEE TRANSMITTAL for FY 2002

Patent fees are subject to annual revision.

Complete if Known

Application Number	09/972,913
Filing Date	October 10, 2001
First Named Inventor	Ashley I. Bush
Examiner Name	To Be Assigned
Group Art Unit	1615
Attorney Docket No.	0609.4540003/JAG/FRC

TOTAL AMOUNT OF PAYMENT

(\$640.00)

METHOD OF PAYMENT (check one)

1. ☐ The Commissioner is hereby authorized to charge indicated fees and credit any overpayment to:

Deposit Account Number

19-0036

Deposit Account Name

Sterne, Kessler, Goldstein & Fox P.L.L.C.

- ☒ Charge Any Additional Fee Required Under 37 CFR §§ 1.16 and 1.17

- ☒ Applicant claims small entity status See 37 CFR 1.27

2. ☒ Payment Enclosed:

☒ Check ☐ Credit card ☐ Money Order ☒ Other*

*Charge any deficiencies or credit any overpayments in the fees or fee calculations of Parts 1, 2 and 3 below to Deposit Account No. 19-0036.

FEE CALCULATION

1. BASIC FILING FEE

Large Fee Code	Entity Fee (\$)	Small Fee Code	Entity Fee (\$)	Fee Description	Fee Paid
101	740	201	370	Utility filing fee	
106	330	206	165	Design filing fee	
107	510	207	255	Plant filing fee	
108	740	208	370	Reissue filing fee	
114	160	214	80	Provisional filing fee	

SUBTOTAL (1) (\$)

2. EXTRA CLAIM FEES

	Extra	Fee from below	Fee Paid
Total Claims _____ - 20** = _____	X		
Indep. Claims _____ - 3** = _____	X		
Multiple Dependent _____			

Large Fee Code	Entity Fee (\$)	Small Fee Code	Entity Fee (\$)	Fee Description
103	18	203	9	Claims in excess of 20
102	84	202	42	Independent claims in excess of 3
104	280	204	140	Multiple dependent claim
108	84	209	42	**Reissue independent claims over original patent
110	18	210	9	**Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) (\$)

** or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Small Entity

Fee Code	Fee (\$)	Fee Code	Fee (\$)	Fee Description	Fee paid
105	130	205	65	Surcharge - late filing fee or oath	
127	50	227	25	Surcharge - late provisional filing fee or cover sheet	
139	130	139	130	Non-English specification	
147	2,520	147	2,520	For filing a request for <i>ex parte</i> reexamination	
112	920*	112	920*	Requesting publication of SIR prior to Examiner action	
113	1,840*	113	1,840*	Requesting publication of SIR after Examiner action	
115	110	215	55	Extension for reply within first month	
116	400	216	200	Extension for reply within second month	
117	920	217	460	Extension for reply within third month	
118	1,440	218	720	Extension for reply within fourth month	
128	1,960	228	980	Extension for reply within fifth month	
119	320	219	160	Notice of Appeal	
120	320	220	160	Filing a brief in support of an appeal	
121	280	221	140	Request for oral hearing	
138	1,510	138	1,510	Petition to institute a public use proceeding	
140	110	240	55	Petition to revive - unavoidable	
141	1,280	241	640	Petition to revive - unintentional	640.00
142	1,280	242	640	Utility issue fee (or reissue)	
143	460	243	230	Design issue fee	
144	620	244	310	Plant issue fee	
122	130	122	130	Petitions to the Commissioner	
123	130	123	130	Petitions related to provisional applications	
126	180	126	180	Submission of Information Disclosure Stmt	
581	40	481	40	Recording each patent assignment per property (times number of properties)	
146	740	246	370	Filing a submission after final rejection (37 CFR 1.129(a))	
149	740	249	370	For each additional invention to be examined (37 CFR 1.129(b))	
179	740	279	370	Request for Continued Examination (RCE)	
169	900	169	900	Request for expedited examination of a design application	

Other fee (specify):

Other fee (specify):

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) (\$640.00)

SUBMITTED BY

Complete (if applicable)

Name (Print/Type)	Frank R. Cottingham	Registration No. (Attorney/Agent)	50,437	Telephone	202-371-2600
Signature	Frank R. Cottingham	Date	7/24/02		

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

Burden Hour Statement: This form is estimated to take 0.2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

BUSH *et al.*

Appl. No. 09/972,913

Filed: October 10, 2001

For: **Use of Clioquinol for the Therapy
of Alzheimer's Disease**

Confirmation No. 5681

Art Unit: 1615

Examiner: *To be assigned*

Atty. Docket: 0609.4540003/JAG/FRC

Request for Reconsideration of Petition Under 37 C.F.R. § 1.47(a)

Commissioner for Patents
Washington, D.C. 20231

COPY

Sir:

In reply to the Decision Refusing Status Under 37 C.F.R. § 1.47(a) dated **February 11, 2002**, (PTO Prosecution File Wrapper Paper No. 3), the period for reply having been extended five (5) months by petition and payment of the appropriate fee, Applicants submit the following Request for Reconsideration.

The Decision Refusing Status Under 37 C.F.R. § 1.47(a) indicates that Applicants have met all of the requirements under 37 C.F.R. § 1.47(a) except for the requirement that a declaration which complies with 37 C.F.R. § 1.63 be submitted with the "Rule 47" petition. *See* Paper No. 3, page 2, lines 14-16. More specifically, it is asserted that the declaration that was submitted to inventor Xilinas "fails to list the residence, citizenship, or post office address of inventor Cherny." *See* Paper No. 3, page 2, lines 17-19. It is further indicated that, upon renewed petition, Applicants should either provide the signature of the non-signing inventor (Xilinas), or provide a showing that a declaration which complies with 37 C.F.R. § 1.63 has been submitted to the non-signing inventor for his review. *See* Paper No. 3, page 2, lines 20-22.

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OFFICE OF PETITIONS

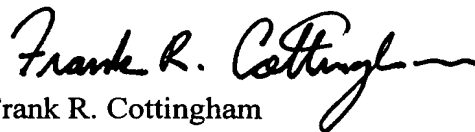
Accordingly, submitted herewith is an Affidavit signed by Frank R. Cottingham, attorney for Applicants, asserting that a declaration which complies with 37 C.F.R. § 1.63 has been submitted to Dr. Xilinas for his review. Applicants believe that the facts stated in the attached Affidavit, along with its Exhibits, establish that a Declaration for Patent Application which complies with 37 C.F.R. § 1.63 was presented to Dr. Xilinas for his review and that a *bona fide* attempt was made to obtain his signature thereon.

It is not believed that extensions of time are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor are hereby authorized to be charged to our Deposit Account No. 19-0036.

Applicants believe that a full and complete reply has been made to the outstanding Decision Refusing Status Under 37 C.F.R. § 1.47(a). Applicants therefore respectfully request that the Decision Refusing Status be reconsidered and that Applicants' Petition Under 37 C.F.R. § 1.47(a) be granted.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Frank R. Cottingham
Attorney for Applicants
Registration No. 50,437

Date: 9/11/02

1100 New York Avenue, N.W.
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Confirmation No. 5681

Art Unit: 1615

Examiner: *To be assigned*

Atty. Docket: 0609.4540003/JAG/FRC

**Affidavit in Support of Request for Reconsideration of Petition
Under 37 C.F.R. § 1.47(a)**

Commissioner for Patents
Washington, D.C. 20231

COPY

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SEP 26 2002

OFFICE OF PETITIONS

Sir:

I, the undersigned, Frank R. Cottingham, hereby declare and state that:

1. I am attorney for The General Hospital Corporation, the assignee of the above-captioned patent application.
2. I have read and understand 37 C.F.R. §§ 10.18(b) and (c).
3. Michel¹ Xilinas has been named as an inventor on the above-captioned patent application.
4. On July 25, 2002, the following items were sent by Federal Express to Dr. Xilinas at his then last-known address, 15 Atalante, 145 63 Kisifia, Greece:
 - (a) Cover letter (copy included herewith as Exhibit A);
 - (b) Copy of the above-captioned patent application (copy included herewith as Exhibit B);

¹At the time the above-captioned application was filed, it was believed that the correct spelling of inventor Xilinas' first name was "Mikhal." It was subsequently discovered that the correct spelling of his first name is Michel.

- (c) Copy of the Preliminary Amendment that was filed with the application (copy included herewith as Exhibit C);
- (d) Declaration for Patent Application that complies with 37 C.F.R. § 1.63 (copy included herewith as Exhibit D); and
- (e) Copy of 37 C.F.R. §§ 10.18(b) and (c) (copy included herewith as Exhibit E).

5. On August 8, 2002, a Federal Express tracking report was obtained by the undersigned indicating that, on July 31, 2002, the Federal Express package containing the above-listed items was successfully delivered and signed for. A copy of the tracking report is included herewith as Exhibit F.

6. On August 8, 2002, an electronic mail (e-mail) message purportedly sent by Dr. Xilinas was received by the undersigned. The message indicated that Dr. Xilinas had received the Federal Express package of July 25, 2002. The message also indicated that Dr. Xilinas would be sending the documents in the Federal Express package to Dr. Xilinas' lawyer, Mr. Georgopoulos, but that Mr. Georgopoulos' law office was closed for the August vacations. The message further stated that Dr. Xilinas is a French citizen, that the correct spelling of his first name is Michel (not Mikhal) and that he is a resident of Larnaca, Cyprus. A copy of the August 8, 2002 e-mail message is included herewith as Exhibit G.

7. On September 6, 2002, a second e-mail message purportedly sent by Dr. Xilinas was received by the undersigned. Attached to the e-mail message was a letter from Dimitri M. Georgopoulos addressed to the undersigned. In the letter, Mr. Georgopoulos requested that I provide him (Mr. Georgopoulos) with "the necessary background information" including information regarding the "pending legal case between Prana, MGH

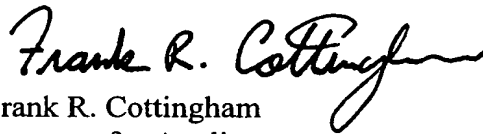
and P.N. Gerolymatos." A copy of the September 6, 2002 e-mail message, including the attachment from Mr. Georgopoulos, is included herewith as Exhibit H.

8. In response to Mr. Georgopoulos' request for information, copies of the complaint and answer that were filed in the litigation between Prana Biotechnology, Ltd *et al.* and P.N. Gerolymatos S.A., were sent to Mr. Georgopoulos via facsimile on September 10, 2002. A copy of the documents that were sent via facsimile to Mr. Georgopoulos is included herewith as Exhibit I.

9. As of the date indicated below, no further communication has been received from either Dr. Xilinas or Mr. Georgopoulos.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Frank R. Cottingham
Attorney for Applicants
Registration No. 50,437

Date: 9/11/02

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
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*Admitted only in Maryland
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September 10, 2002

WRITER'S DIRECT NUMBER:

(202) 371-2615

INTERNET ADDRESS:

FRANKC@SKGF.COM

Mr. Dimitri M. Georgopoulos
Advocate
45 Koniari Str.
11471 Athens
GREECE

via Facsimile

DUPLICATE

Re: U.S. Utility Patent Application
Appl. No. 09/972,913; Filed: October 10, 2001
For: Use of Clioquinol for the Therapy of Alzheimer's Disease
Inventors: BUSH *et al.*
GH Ref: VS:SDT:GF35003:GM25371
MGH Ref: 1290.3
Our Ref: 0609.4540003/JAG/FRC

Dear Mr. Georgopoulos:

Further to your letter which was attached to Dr. Xilinas' September 6, 2002 e-mail, enclosed please find a copy of the complaint and answer that were filed in connection with the litigation between Prana Biotechnology, Ltd. *et al.* and P.N. Gerolymatos S.A. We would appreciate a response to our request for Dr. Xilinas' signature on the Declaration for the above-captioned patent application as soon as possible, preferably by **September 11, 2002**. If you have any questions regarding this matter, please do not hesitate to contact me.

Very truly yours,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Frank R. Cottingham
Frank R. Cottingham

FRC/pcd
Enclosures

cc: Dr. Colm Lawler (w/encls.)
Dr. Simon Tout (w/encls.)

SKGF_DC1:53736.1



Robert Greene Sterne
Edward J. Kessler
Jorge A. Goldstein
David K.S. Cornwell
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Lisa A. Dunner

* Admitted only in Maryland
* Admitted only in Virginia
* Admitted only in Texas
* Practice Limited to
Federal Agencies

July 25, 2002

WRITER'S DIRECT NUMBER:
(202) 371-2615

INTERNET ADDRESS:
FAX@SKGF.COM

FILE COPY

Via Federal Express

400-32663400

Dr. Mikhal Xilinas
15 Atalante
145 63 Kisifia
GREECE

Re: U.S. Utility Patent Application
Appl. No. 09/972,913; Filed: October 10, 2001
For: **Use of Clioquinol for the Therapy of Alzheimer's Disease**
Inventors: BUSH *et al.*
MGH Ref: 1290.3 CON
GH Ref: GF 35003:GM 25371
Our Ref: 0609.4540003/JAG/FRC

RECEIVED

SEP 26 2002

OFFICE OF PETITIONS

Dear Dr. Xilinas:

We believe that you are a co-inventor of the subject matter of at least one of the claims in the above-captioned U.S. patent application. Enclosed please find a copy of the application as filed and a copy of the Preliminary Amendment that was filed with the application.

Also, enclosed please find a Declaration for Patent Application. The Declaration states that the party signing it is an original, first and joint inventor of the subject matter claimed in the application. In order to complete the formalities for the patent application filed in the U.S. Patent and Trademark Office (USPTO), we must attempt to obtain the signatures of each of the inventors. Therefore, we ask that you sign and return this document, if, after careful consideration, you believe yourself to be a co-inventor of at least one of the claims in the application.

Please note that every person who signs a document that is submitted to the USPTO makes a certification under USPTO regulation 37 CFR § 10.18(b). A copy of 37 CFR § 10.18(b) and (c) is attached. Therefore, you should review this regulation prior to signing the Declaration.

Dr. Mikhal Xilinas

July 25, 2002

Page 2

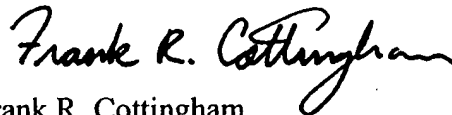
Please carefully review the Declaration and the information we have entered into it. Please add any missing information using **blue ink**. By "Residence" is meant the city and state of your residence, or if the residence is outside the U.S., the city and country of the residence. The "Post Office address" is the full address at which you customarily receive your mail.

After you have reviewed the Declaration, and any necessary corrections have been made, please sign and date the document using **blue ink**. Your signature and the date should be placed next to the check marks that appear after the phrase "Signature of third inventor."

We request that you respond to this letter as soon as possible, and preferably by **August 19, 2002**, regardless of whether you agree to sign the Declaration. If you have any questions, or if the documents do not appear to be in order, please contact us immediately.

Very truly yours,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Frank R. Cottingham

FRC/pcd
Enclosures

cc: Colm Lawler, Ph.D.
Vivien Santer, Ph.D.

SKGF_DC1:4901.1



Robert Greene Sterne
Edward J. Kessler
Jorge A. Goldstein
David K.S. Cornwell
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SEP 24 2002
PATENT & TRADEMARK OFFICE
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*Admitted only in Texas
*Practice Limited to Federal Agencies

September 11, 2002

WRITER'S DIRECT NUMBER:

(202) 371-2615

INTERNET ADDRESS:

FRANKC@SKGF.COM

COPY

Commissioner for Patents
Washington, D.C. 20231

Box DAC

Re: U.S. Utility Patent Application
Appl. No. 09/972,913; Filed: October 10, 2001
For: Use of Clloquinol for the Therapy of Alzheimer's Disease
Inventors: BUSH *et al.*
Our Ref: 0609.4540003/JAG/FRC

Sir:

Transmitted herewith for appropriate action are the following documents:

1. Fee Transmittal Form (PTO/SB/17);
2. Petition for Extension of Time Under 37 C.F.R. § 1.136(a)(1);
3. Request for Reconsideration of Petition Under 37 C.F.R. § 1.47(a);
4. Affidavit in Support of Request for Reconsideration of Petition Under 37 C.F.R. § 1.47(a) along with Exhibits A-I;
5. Our check no. **36617** in the amount of **\$980.00** to cover the extension of time fee (*5 months*); and
6. Return postcard.

It is respectfully requested that the attached postcard be stamped with the date of filing of these documents, and that it be returned to our courier. In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

Commissioner for Patents
September 11, 2002
Page 2



The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

A handwritten signature in cursive script that reads "Frank R. Cottingham".

Frank R. Cottingham
Attorney for Applicants
Registration No. 50,437

FRC/pcd
Enclosures

::ODMAMHODMA\SKGF_DC1;54562;1

STERNE, KESSLER, GOLDSTEIN & FOX PLLC
ATTORNEYS AT LAW
GOVERNMENT FEES ACCT.
1100 NEW YORK AVE. NW, SUITE 600
WASHINGTON, D.C. 20005

REMITTANCE ADVICE			

36617

15-122

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9/11/02	COMM. OF PATENTS & TRADEMARKS

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COPY

Due Date: September 11, 2002

Art Unit: 1615

Examiner: To be assigned

Docket: 0609.4540003

Atty: JAG/FRC

Applicants: BUSH *et al.*

Application No.: 09/972,913

Filed: October 10, 2001

For: Use of Clloquinol for the Therapy of Alzheimer's Disease

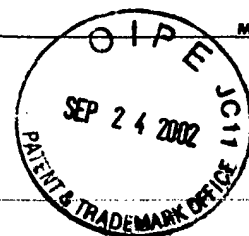
When receipt stamp is placed hereon, the USPTO acknowledges receipt of the following documents:

1. SKGF Cover Letter;
2. Fee Transmittal Form (PTO/SB/17);
3. Petition for Extension of Time Under 37 C.F.R. § 1.136(a)(1);
4. Request for Reconsideration of Petition Under 37 C.F.R. § 1.47(a);
5. Affidavit in Support of Request for Reconsideration of Petition Under 37 C.F.R. § 1.47(a) along with Exhibits A-I;
6. Our check no. 36617 in the amount of \$980.00 to cover the extension of time fee (5 months); and
7. Return postcard.

Box DAC

Please Date Stamp And Return To Our Courier

SKGF_DC1:54576.1





COPY

Applicants: BUSH *et al.*

Due Date: September 11, 2002
Art Unit: 1615

Application No.: 09/972,913

Examiner: To be assigned
Docket: 0609.4540003

Filed: October 10, 2001

Atty: IAG/FRC

For: Use of Clloquinol for the Therapy of Alzheimer's Disease

When receipt stamp is placed hereon, the USPTO acknowledges receipt of the following documents:

1. SKGF Cover Letter;
2. Fee Transmittal Form (PTO/SB/17);
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6. Our check no. 36617 in the amount of \$980.00 to cover the extension of time fee (5 months); and
7. Return postcard.



SKGF_DC1:34576.1

Please Date Stamp And Return To Our Courier

Box DAC

Exhibit A



Robert Greene Sterne
Edward I. Kessler
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David K.S. Cornwell
Robert W. Edmund
Tracy-Gene G. Durkin
Michael A. Cimbalà
Michael B. Ray
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*Admitted only in Maryland
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*Practice Limited to
Federal Agencies

July 25, 2002

WRITER'S DIRECT NUMBER:
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E-MAIL: SKG@SKGF.COM

FILE COPY

Dr. Mikhal Xilinas
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145 63 Kisifia
GREECE

Via Federal Express

400-32663400

Re: U.S. Utility Patent Application
Appl. No. 09/972,913; Filed: October 10, 2001
For: Use of Clloquinol for the Therapy of Alzheimer's Disease
Inventors: BUSH *et al.*
MGH Ref: 1290.3 CON
GH Ref: GF 35003:GM 25371
Our Ref: 0609.4540003/JAG/FRC

Dear Dr. Xilinas:

We believe that you are a co-inventor of the subject matter of at least one of the claims in the above-captioned U.S. patent application. Enclosed please find a copy of the application as filed and a copy of the Preliminary Amendment that was filed with the application.

Also, enclosed please find a Declaration for Patent Application. The Declaration states that the party signing it is an original, first and joint inventor of the subject matter claimed in the application. In order to complete the formalities for the patent application filed in the U.S. Patent and Trademark Office (USPTO), we must attempt to obtain the signatures of each of the inventors. Therefore, we ask that you sign and return this document, if, after careful consideration, you believe yourself to be a co-inventor of at least one of the claims in the application.

Please note that every person who signs a document that is submitted to the USPTO makes a certification under USPTO regulation 37 CFR § 10.18(b). A copy of 37 CFR § 10.18(b) and (c) is attached. Therefore, you should review this regulation prior to signing the Declaration.

Dr. Mikhal Xilinas

July 25, 2002

Page 2

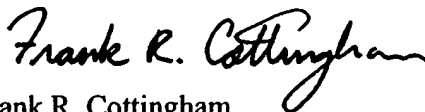
Please carefully review the Declaration and the information we have entered into it. Please add any missing information using **blue ink**. By "Residence" is meant the city and state of your residence, or if the residence is outside the U.S., the city and country of the residence. The "Post Office address" is the full address at which you customarily receive your mail.

After you have reviewed the Declaration, and any necessary corrections have been made, please sign and date the document using **blue ink**. Your signature and the date should be placed next to the check marks that appear after the phrase "Signature of third inventor."

We request that you respond to this letter as soon as possible, and preferably by **August 19, 2002**, regardless of whether you agree to sign the Declaration. If you have any questions, or if the documents do not appear to be in order, please contact us immediately.

Very truly yours,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



Frank R. Cottingham

FRC/pcd
Enclosures

cc: Colm Lawler, Ph.D.
Vivien Santer, Ph.D.

SKGF_DC1:4901.1

Exhibit B

Use of Clioquinol for the Therapy of Alzheimer's Disease

Background of the Invention

Field of the Invention

5 This invention is in the field of medicinal chemistry. In particular, the invention is related to the use of clioquinol for therapy of Alzheimer's disease.

Related Art

10 Polymers of Abeta ($A\beta$), the 4.3 kD, 39-43 amino acid peptide product of the transmembrane protein, amyloid protein precursor (APP), are the main components extracted from the neuritic and vascular amyloid of Alzheimer's disease (AD) brains. $A\beta$ deposits are usually most concentrated in regions of high neuronal cell death, and may be present in various morphologies, including amorphous deposits, neurophil. plaque amyloid, and amyloid congophilic angiopathy (Masters, C.L., *et al.*, *EMBO J.* 4:2757 (1985); Masters, C.L. *et al.*, *Proc. Natl. Acad. Sci. USA* 82: 4245 (1985)). Growing evidence suggests that
15 amyloid deposits are intimately associated with the neuronal demise that leads to dementia in the disorder.

20 The presence of an enrichment of the 42 residue species of $A\beta$ in these deposits suggests that this species is more pathogenic. The 42 residue form of $A\beta$ ($A\beta_{1-42}$), while a minor component of biological fluids, is highly enriched in amyloid, and genetic studies strongly implicate this protein in the etiopathogenesis of AD. To date, the cause of $A\beta$ deposits is unknown, although it is believed that preventing these deposits may be a means of treating the disorder.

25 Studies into the neurochemical vulnerability of $A\beta$ to form amyloid have suggested altered zinc and $[H^+]$ homeostasis as the most likely explanations for amyloid deposition. $A\beta$ is rapidly precipitated under mildly acidic conditions *in vitro* (pH 3.5-6.5) (Barrow, C.J. & Zagorski, M.G., *Science* 253:179-182 (1991); Fraser, P.E., *et al.*, *Biophys. J.* 60:1190-1201 (1991); Barrow, C.J., *et al.*,

J. Mol. Biol. 225:1075-1093 (1992); Burdick, D., *J. Biol. Chem.* 267:546-554 (1992); Zagorski, M.G. & Barrow, C.J., *Biochemistry* 31:5621-5631 (1992); Kirshenbaum, K. & Daggett, V., *Biochemistry* 34:7629-7639 (1995); Wood, S.J., *et al.*, *J. Mol. Biol.* 256:870-877 (1996)). Recently, it has been shown that the presence of certain biometals, in particular redox inactive Zn^{2+} and, to a lesser extent, redox active Cu^{2+} and Fe^{3+} , markedly increases the precipitation of soluble $A\beta$ (Bush, A.T., *et al.*, *J. Biol. Chem.* 268:16109 (1993); Bush, A.I., *et al.*, *J. Biol. Chem.* 269:12152 (1994); Bush, A.I., *et al.*, *Science* 265:1464 (1994); Bush, A.I., *et al.*, *Science* 268:1921 (1995)). At physiological pH, $A\beta_{1-40}$ specifically and saturably binds Zn^{2+} , manifesting high affinity binding ($K_D = 107$ nM) with a 1:1 ($Zn^{2+}:A\beta$) stoichiometry, and low affinity binding ($K_D = 5.2$ μ M) with a 2:1 stoichiometry.

Clioquinol (iodochlorhydroxyquin, 5-chloro-7-iodo-8-hydroxyquinoline, MW 305.5) is a USP drug that chelates zinc [$K(Zn) = 12.5$, $K(Cu) = 15.8$, $K(Ca) = 8.1$, $K(Mg) = 8.6$], is hydrophobic, has a low general toxicity profile, and crosses the blood brain barrier (Padmanabhan *et al.*, 1989). It has been used as an oral anti-amebic antibiotic, and as a topical antibiotic.

It has been demonstrated that clioquinol is rapidly absorbed from the gut of rats and mice where blood levels reached $\approx 1 \cdot 10^{-6}$ μ M within one hour of ingestion (Kotaki *et al.*, *J Pharmacobiodyn*, 6(11):881-887 (1983)). Since the drug is hydrophobic, it passes rapidly into the brain, and then is rapidly excreted, so that a bolus dose of clioquinol is almost completely removed from the brain within three hours. It appears to be safe in many mammalian species, including rat and mouse (Tateishi *et al.*, 1972; Tateishi *et al.*, 1973), and is still used as a veterinary antibiotic (Entero Vioform).

Clioquinol was withdrawn from use as an oral antibiotic for humans in the early 1970's when its ingestion in Japan was linked to a mysterious condition called subacute myelo-optic neuritis (SMON), a condition that resembles subacute combined degeneration of the cord caused by vitamin B12 deficiency. The mechanism of SMON has never been elucidated, but in the 1970's a considerable

literature developed exploring the pathophysiology of clioquinol ingestion (Tateishi *et al.*, 1972; Tateishi *et al.*, 1973). Several reports have demonstrated that clioquinol complexes with zinc in the brain, especially in areas enriched in synaptic vesicular zinc such as the temporal lobe (Shiraki, H. *Handbook of Clinical Neurology*, Vol. 37 (1979)). Indeed, over ingestion of clioquinol has been reported to induce amnesia in humans (Shiraki, H. *Handbook of Clinical Neurology*, Vol: 37 (1979)).

Summary of the Invention

The first aspect of the invention relates to a method for the therapy of amyloidosis comprising administering to a patient in need thereof an effective amount of clioquinol. Clioquinol may be administered alone or in combination with Vitamin B12 and/or trace metals.

The amount of clioquinol administered may be between about 10-250 milligram per kilogram body weight of the patient. Preferably, however, 3-15 mg/kg body weight, and most preferably 5-10 mg/kg body weight is administered.

Vitamin B12 may be administered at any amounts customary for Vitamin B12 supplementation. However, it is preferred to administer about 5-15 milligram, most preferably 7-10 milligram, Vitamin B12 per kilogram body weight of said patient per day if administered orally. When administered intramuscularly, about 50-150 microgram, most preferably 70-100 microgram, Vitamin B12 per kilogram body weight of said patient per month is sufficient.

Trace metals may be supplemented at the customary supplementation levels up to the limits of toxicity. Trace metal administration as well as Vitamin B12 supplementation may be done concurrently with the administration of clioquinol or subsequent thereto during a wash out period.

Clioquinol may be administered alone or in combination with Vitamin B12 and/or the trace metals, parenterally, e.g. intradermally, or orally. It is preferred that clioquinol administration be carried out intermittently, not allowing sustained levels of the drug concentration for extended periods of time.

The duration of therapy may last up to 10 years, preferably 12 months in case of moderately affected individuals. In case of severely affected patients with low quality of life, 1-21 days, preferably 14 days, using high doses of clioquinol. The method of claim 1, wherein the therapy is carried out up to 10 years.

Brief Description of the Figures

Figure 1 is a graphical representation of resolubilization of Zn, Cu, or pH induced aggregates *in vitro*. Values are expressed as a percentage of A β signal after washing with TBS alone.

Figure 2 shows extraction of A β from brain tissue with clioquinol. Undiluted (100%) clioquinol is 1.6 μ M. S1 and S2 represent two sequential extractions from AD-affected tissue.

Figures 3A and 3B: Figure 3A shows a western blot of A β extracted from brain tissue by various concentrations of clioquinol. Figure 3B is a graphic representation of solubilization of A β by clioquinol.

Figure 4 shows a bar graph demonstrating that clioquinol effectively dissolving A β aggregates. A β ₁₋₄₀ was incubated with no metal, Zn (II), Zn (II) + clioquinol, DMSO or clioquinol (120 μ M) in 20 mM HEPES, 150 mM NaCl, pH 7.4. Samples were incubated for 30 minutes at 37°C and then centrifuged at 10,000 g for 20 minutes and the protein content of the supernatant determined using the BCA assay. Clioquinol was dissolved in DMSO prior to adding 20 μ M to the samples. Clioquinol attenuated Zn-induced A β ₁₋₄₀ aggregation. DMSO had no effect on A β aggregation. Results are mean \pm SD, n = 3.

Detailed Description of the Preferred Embodiments

Definitions

In the description that follows, a number of terms are utilized extensively. In order to provide a clear and consistent understanding of the specification and

claims, including the scope to be given such terms, the following definitions are provided.

5 $A\beta$ peptide is also known in the art as $A\beta$, β protein, β -A4 and A4. In the present invention, the $A\beta$ peptide may be comprised of peptides $A\beta_{1-39}$, $A\beta_{1-40}$, $A\beta_{1-41}$, $A\beta_{1-42}$, and $A\beta_{1-43}$. The most preferred embodiment of the invention makes use of $A\beta_{1-40}$. However, any of the $A\beta$ peptides may be employed according to the present invention. The sequence of $A\beta$ peptide is found in Hilbich, C., *et al.*, *J. Mol. Biol.* 228:460-473 (1992).

10 Amyloid as is commonly known in the art, and as is intended in the present specification, is a form of aggregated protein.

 Amyloidosis is any disease characterized by the extracellular accumulation of amyloid in various organs and tissues of the body.

$A\beta$ Amyloid is an aggregated $A\beta$ peptide. It is found in the brains of patients afflicted with AD and DS and may accumulate following head injuries.

15 Zinc, unless otherwise indicated, means salts of zinc, i.e., Zn^{2+} in any form, soluble or insoluble.

 Wash Out Period, unless otherwise indicated, means the relatively prolonged period between two administrations of clioquinol, during which clioquinol is cleared from patient's body. Wash out period may last between one
20 to four weeks.

25 Considerable evidence now indicates that the accumulation of $A\beta$ in the brain cortex is very closely related to the cause of Alzheimer's disease. $A\beta$ is a normal component of biological fluids whose function is unknown. $A\beta$ accumulates in a number of morphologies varying from highly insoluble amyloid to deposits that can be extracted from post-mortem tissue in aqueous buffer. The factors behind the accumulation are unknown, but the solubility of synthetic $A\beta$ peptide has been systematically appraised in order to get some clues as to what kind of pathological environment could induce the peptide to precipitate.

Direct evidence has been obtained that show zinc and copper to be integral components of the A β deposits in the brain in AD. It is disclosed herein that clioquinol, a zinc- and copper-specific chelator, dramatically re-dissolves a significant proportion (up to 70%) of A β extracted from post-mortem AD affected brain tissue, compared to the amount extracted from the tissue by buffer in the absence of chelators. These data support a strategy of re-dissolving A β deposits *in vivo* by chelation with clioquinol.

The growing evidence in the art indicates that in AD patients, physiological levels of zinc aggregate A β and result in precipitation of the same and formation of amyloid deposits. Although one may speculate as to using chelators of zinc to prevent zinc from aggregating and precipitating A β in the brain, it is not clear whether A β amyloids can be dis-aggregated and re-dissolved into the biological fluid in the surrounding brain milieu. Therefore, the present discovery that clioquinol is capable of dissolving A β amyloid is a significant step towards designing a drug for the therapy of Alzheimer's Disease, and perhaps Dawn Syndrom and other conditions caused by formation of such aggregates, causing amyloidosis.

Accordingly, the present invention is directed to clioquinol as such therapeutic agent. Results of experiments, presented herein, demonstrate that clioquinol is capable of dis-aggregating A β amyloid deposits.

Clioquinol (iodochlorhydroxyquin, 5-chloro-7-iodo-8-hydroxyquinoline, MW 305.5) is a USP drug that chelates zinc [$K(\text{Zn})=12.5$, $K(\text{Cu})=15.8$, $K(\text{Ca})=8.1$, $K(\text{Mg})=8.6$], is hydrophobic, has a low general toxicity profile, and crosses the blood brain barrier (Padmanabhan *et al.*, 1989). It therefore possesses some of the ideal prototypic properties for an agent for solubilization of zinc-assembled A β deposits *in vivo*. It has been used as an oral anti-ameobic antibiotic, and as a topical antibiotic.

It has been demonstrated that clioquinol is rapidly absorbed from the gut of rats and mice where blood levels reached $\approx 1-10 \mu\text{M}$ within one hour of ingestion (Kotaki *et al.*, *J Pharmacobiodyn*, 6(11):881-887 (1983)). Since the

drug is hydrophobic, it passes rapidly into the brain, and then is rapidly excreted, so that a bolus dose of clioquinol is almost completely removed from the brain within three hours. It appears to be safe in many mammalian species, including rat and mouse (Tateishi *et al.*, 1972; Tateishi *et al.*, 1973), and is still used as a veterinary antibiotic (Entero Vioform).

Clioquinol was withdrawn from use as an oral antibiotic for humans in the early 1970's when its ingestion in Japan was linked to a mysterious condition called subacute myelo-optic neuritis (SMON), a condition that resembles subacute combined degeneration of the cord caused by vitamin B12 deficiency. The mechanism of SMON has never been elucidated, but in the 1970's a considerable literature developed exploring the pathophysiology of clioquinol ingestion (Tateishi *et al.*, 1972; Tateishi *et al.*, 1973). Several reports have demonstrated that clioquinol complexes with zinc in the brain, especially in areas enriched in synaptic vesicular zinc such as the temporal lobe (Shiraki, H. *Handbook of Clinical Neurology*, Vol. 37 (1979)). Indeed, over ingestion of clioquinol has been reported to induce amnesia in humans (Shiraki, H. *Handbook of Clinical Neurology*, Vol. 37 (1979)).

Clioquinol has a relatively safe profile in mice, and there is a large literature on its pharmacology in this animal. It is disclosed herein data regarding its ability to specifically chelate zinc from A β deposits *in vitro* (induced aggregates and brain samples). Based on the *in vitro* data described herein, it is reasonably expected that the low concentrations of clioquinol shown to be effective in resolubilizing A β in the present invention may avoid the adverse SMON effect noted above. Thus, given its other pharmacological properties, clioquinol holds promise as an effective agent in the treatment of AD in humans.

It has been found that there is a clioquinol concentration "window" within which the A β aggregates are dissolved. Increasing the concentration of clioquinol above the window not only is toxic to the patient but also sharply drops the dissolution effect of clioquinol on the A β amyloid. Similarly, amounts below that of the window are too small to result in any dissolution.

Therefore, for each given patient, the attending physician need be mindful of the window effect and attend to varying the dosages of clioquinol so that during the course of administration, clioquinol concentrations would be varied frequently to randomly allow achieving the most effective concentration for dissolving A β amyloid deposits in the given patient.

It is, therefore, desired that the plasma levels of clioquinol not be steady state, but be kept fluctuating between 0.01 μ M, but not greater than 2 μ M. Since the drug is absorbed to reach peak plasma levels within 30 minutes of oral ingestion, and since the excretion half life is about 1-3 hours, the best way to dose the patient is with oral doses no more often than every three hours, preferably every six hours or eight hours, but as infrequently as once every day or once every two days are expected to be therapeutic.

An oral dose of 200 mg/kg achieves 5 μ M plasma levels in rats, and 10-30 μ M in dogs. An oral dose of 500 mg/kg achieves 20-70 μ M in monkeys. The drug is freely permeable into the brain and is rapidly excreted.

Therefore, in humans, it is expected that a plasma level of 0.5 μ M would be achieved within 30 minutes of ingesting 10 mg/kg body weight. In a 70 kg person this is 700 mg of clioquinol. Therefore, a dose of 700 mg four times a day (2800 mg/day) would be therapeutic.

However, sustained treatment with doses of clioquinol at a dose as low as 10 mg/kg/day causes the neurological side effect, subacute myelo-optic neuritis. Therefore, dosage that high is undesirable. This is equivalent to 700 mg/day. The side effect is believed to be due to loss of vitamin B12. Therefore, co-therapy with vitamin B12 100 μ M/day orally or, preferably, 1000 μ M/month intramuscularly, is to be administered with clioquinol treatment to abolish this side effect.

To minimize the chances of this side effect, a lower dose of clioquinol can also be used - 100 mg, three or four times a day would achieve peak plasma levels of about 0.1 μ M, and is likely to be therapeutic without putting the patient at risk

for neurological side effects. Nevertheless, co-administration of Vitamin B12 should be mandatory.

For the treatment of moderately affected or severely affected patients, where risking the neurological side effects is less of a concern since the quality of their life is very poor, the patient may be put on a program of treatment (after informed consent) consisting of high dose clioquinol for 1 to 21 days, but preferably no more than 14 days, followed by a period of low dose therapy for seven days to three months. A convenient schedule would be two weeks of high dose therapy followed by two weeks of low dose therapy, oscillating between high and low dose periods for up to 12 months. If after 12 months the patient has made no clinical gains on high/low clioquinol therapy, the treatment should be discontinued. All regiments would be accompanied by Vitamin B12 co-therapy.

Another typical case would be the treatment of a mildly affected individual. Such a patient would be treated with low dose clioquinol for up to 12 months. If after 6 months no clinical gains have been made, the patient could then be placed on the high/low alternation regimen for up to another 12 months.

Accordingly, the present invention contemplates compositions such as pharmaceutical compositions comprising an active agent and one or more pharmaceutically acceptable carriers and/or diluents. The active agent may be clioquinol or a combination of clioquinol and another metal chelating compound.

The pharmaceutical forms containing the active agents may be administered in any convenient manner such as by intravenous, intraperitoneal, subcutaneous, rectal, implant, transdermal, slow release, intrabuccal, intracerebral or intranasal administration. Generally, the active agents need to pass the blood brain barrier and may have to be chemically modified to facilitate this or be administered directly to the brain or *via* other suitable routes. For injectable use, sterile aqueous solutions (where water soluble) are generally used or alternatively sterile powders for the extemporaneous preparation of sterile injectable solutions may be used. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such

as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The preventions of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active agents in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by sterilization by, for example, filtration or irradiation. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze-drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof. Preferred compositions or preparations according to the present invention are prepared so that an injectable dosage unit contains enough clioquinol to raise the plasma concentration of clioquinol in the subject, the patient, to about between 0.01-1 μ M.

When the active agents are suitably protected they may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsule, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, the active compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 1% by weight of active compound. The percentage of the compositions and preparations may, of course,

be varied and may conveniently be between about 5 to about 80% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 10 mg and 1000 mg, preferably 50-500 mg, and most preferably 200-500 mg of clioquinol.

The tablets, troches, pills, capsules and the like may also contain other components such as listed hereafter: A binder such as gum, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound(s) may be incorporated into sustained-release preparations and formulations.

Pharmaceutically acceptable carriers and/or diluents include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, use thereof in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the novel dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active material for the treatment of disease in living subjects having a diseased condition in which bodily health is impaired as herein disclosed in detail.

The principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore disclosed. A unit dosage form can, for example, contain the principal active compound in amounts ranging from 10mg to about 2000 mg. Alternatively, amounts ranging from 1 mg/kg body weight to above 20 mg/kg body weight may be administered. Preferably, however, the amount of the principal active ingredient, clioquinol, is about 3-15 mg/kg body weight, most preferably about 5-10 mg/kg body weight. The amounts may be for individual active agents or for the combined total of active agents.

Compositions of the present invention include all compositions wherein the compounds of the present invention are contained in an amount which is effective to achieve their intended purpose. They may be administered by any means that achieve their intended purpose. The dosage administered will depend on the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of the treatment, and the nature of the effect desired. The dosage of the various compositions can be modified by comparing the relative *in vivo* potencies of the drugs and the bioavailability using no more than routine experimentation.

The pharmaceutical compositions of the invention may be administered to any animal which may experience the beneficial effects of the compounds of the

invention. Foremost among such animals are mammals, e.g., humans, although the invention is not intended to be so limited.

The following examples are provided by way of illustration to further describe certain preferred embodiments of the invention, and are not intended to be limiting of the present invention, unless specified.

Examples

Dissolving Clioquinol

In order to obtain a solution of clioquinol in PBS, the following protocol was followed: 5.3 grams of clioquinol was suspended with agitation in 200 milliliter of n-decane. The undissolved material was settled, air dried, and weighed, based on which it was determined that only 2 % of the clioquinol had dissolved in the n-decane. 100 milliliter of the supernatant (light yellow) was agitated in 100 milliliter of PBS, pH 7.4. Next, the phases were allowed to separate. The lower phase (PBS) was collected and filtered to remove the residue which had formed at the phase interface upon extraction with the organic solvent. The concentration of clioquinol in the PBS was determined to be 800 nanomolar. This number was arrived at based on two assumptions: (1) 2 % of the clioquinol was dissolved in the n-decane; and (2) the partitioning coefficient is 1/1750 with PBS at 1:1 mixture of n-decane to clioquinol.

Example 1

A β Aggregates by C Resolubilization of Metal-induced lioquinol

A β (10 ng/well in TBS) aggregation was induced by addition of ZnCl₂ (25 μ M), CuCl₂ (5 μ M) or acidic conditions (pH 5.5). Aggregates were transferred to a 0.2 μ nylon membrane by filtration. The aggregates were then washed (200

5 $\mu\text{l/well}$) with TBS alone, TBS containing 2 μM EDTA, or TBS containing 2 μM clioquinol. The membrane was fixed, probed with the anti-A β monoclonal antibody 6E10, and developed for exposure to ECL-film. Figure 3A shows relative signal strength as determined by transmittance analysis of the ECL-film, calibrated against known amounts of the peptide. Values are expressed as a percentage of A β signal after washing with TBS alone.

10 Both EDTA and clioquinol treatments were more effective than TBS alone at resolubilizing the retained (aggregated) A β when the peptide was precipitated by Zn or Cu (*see* Fig. 1). When A β was precipitated by pH 5.5 however, it was not resolubilized more readily by either chelator compared to TBS washing alone. The pH 5.5 precipitate contains a much greater proportion of beta-sheet amyloid than the A β precipitates formed by Zn or Cu.

Example 2

A β Extraction from Human Brain Post-Mortem Samples

15 Zinc-mediated A β deposits in human brain have been recently characterized (Cherny, R.A., *et al.*, *Soc. Neurosci Abstr.* 23:(Abstract) (1997)). Also, it was recently reported that there is a population of water-extractable A β deposit in the AD-affected brain (Kuo, Y-M., *et al.*, *J. Biol. Chem.* 271:4077-81 (1996)). It was hypothesized that homogenization of brain tissue in water may dilute the metal content in the tissue, therefore, lowering the putative zinc concentration in A β collections, and liberating soluble A β subunits by freeing A β complexed with zinc [Zn(II)].

20 To test this hypothesis, the brain tissue preparation of Kuo and colleagues was replicated, but phosphate-buffered saline pH 7.4 (PBS) was substituted as the extraction buffer, achieving similar results. Highly sensitive and specific anti-A β monoclonal antibodies (Ida *et al.*, (1996)) were used to assay A β extraction by western blot. Next, the extraction of the same material with PBS was repeated in

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the presence of clioquinol and determined that the presence of clioquinol increased the amount of A β in the soluble extract several-fold (FIGs. 1, 2, 3A, and 3B).

5 The amount of A β detected in the pellet fraction of each sample is correspondingly lower (data not shown), indicating that the effect of clioquinol is upon the disassembly of the A β aggregate, and not by inhibition of an A β -cleaving metalloprotease. The extraction of sedimentable A β into the soluble phase correlated only with the extraction of zinc from the pellet, and not with any other metal assayed. Examination of the total amount of protein released by the treatment revealed that chelation was not merely liberating more proteins in a non-specific manner (data not shown).

Example 3

Resolubilization of A β by Clioquinol

Resolubilization of In Vitro Metal-Induced A β Aggregates

15 First, the efficacy of clioquinol's ability to resolubilize A β aggregates, formed *in vitro* by the action of Cu(II) or Zn(II) upon A β 1-40, was examined. Figure 1 shows resolubilization of metal-induced A β aggregate by chelators. A β (10 ng/well in buffered saline) aggregation was induced by addition of ZnCl₂ (5 μ M) or acidic conditions (pH 5.5). Aggregates were transferred to a 0.2 μ nylon membrane by filtration. The aggregates were then washed (200 μ l/well) with TBS alone, TBS containing 2 μ M EDTA or TBS with 2 μ M clioquinol. The membrane was then fixed, probed with anti-A β monoclonal antibody 6E10 and developed for exposure to ECL-film.

20 Figure 2 shows the relative signal as determined by densitometric analysis of the ECL-film, calibrated against known amounts of the peptide. Values are expressed as a % of A β signal remaining on the filter after washing with TBS alone. Clioquinol is hydrophobic, so that the reagent must first be

solubilized in an organic solvent, and then partitioned into the aqueous buffer according to established protocols (Padmanabhan *et al.*, 1989).

It was found that, like EDTA (FIG. 1), clioquinol significantly resolubilized precipitated A β . Cu(II) partially precipitates A β 1-40 (Bush, A.I., *et al.*, *Science* 268:1921 (1995)) at pH 7.4. It was determined that EDTA (2 μ M) resolubilized 35% of a Zn(II)-induced A β precipitate, 60% of a Cu(II)-induced precipitate, and 15% of a pH 5.5-induced precipitate. In contrast, clioquinol (2 μ M) was more effective at resolubilizing the Zn(II)- and Cu(II)-induced A β precipitates (50%, and 85%, respectively), but was also ineffective at resolubilizing the pH 5.5 precipitate (10%). Since the aggregate at pH 5.5 is predominantly β -sheet (Wood, S.J. *et al.*, *J. Mol. Bio.*, 256:870-877 (1996)), these data indicate that the resolubilization of A β by clioquinol/EDTA is likely to be due to specific chelation effects.

Extraction of A β from Samples of AD-Affected Brains

Next, the ability of clioquinol to extract A β deposits from human brain was determined. It was found that clioquinol efficiently increases the resolubilization of A β , compared to the amount of A β resolubilized from the pellet fraction of brain homogenate by PBS alone. Figure 3 shows the effect of clioquinol upon the extraction of A β from AD-affected brain. Fragments of prefrontal cortex from individual post-mortem samples with the histopathological diagnosis of AD were homogenized in PBS, pH 7.4, and then pelleted after centrifugation.

The pellets were then washed with agitation twice for 30 minutes, 4°C, with PBS or PBS containing clioquinol (100% = 0.8 μ M clioquinol). The suspension was then pelleted (10,000 g for 30 minutes) and the supernatant removed (S1) for western blot analysis using A β -specific antibodies. The pellet was treated a second time in this experiment with agitation and centrifugation, and the second supernatant (S2) analyzed. The data show typical results by western blot.

In agreement with earlier findings which showed that the optimal concentration of chelator for the extraction of A β is idiosyncratic from case to case, and that there is a paradoxical diminution of A β extraction when the chelator concentration rises above the optimum, it was found that optimal clioquinol concentrations for A β resolubilization vary in a similar manner (e.g., Specimen #1= 0.08 μ M, #2= 0.8 μ M). It was also observed that apparently dimeric A β was more frequently observed on SDS-PAGE, and that in these cases (e.g., Specimen #2) the first wash did not resolubilize much A β , but the second wash was very efficient at resolubilizing the peptide. It is surmised that the pellet mass may be coated with adventitial, non-A β , proteins that are removed by the first wash, allowing the second treatment access to the A β collection. Indeed, further studies have shown that both sustained (for 16 hours) and repeated exposure to the chelator increases the resolubilization of A β significantly.

Figure 3A and 3B show the western blot and accompanying densitometric analysis of resolubilization of A β from AD-affected brain. Figure 3A is a western blot showing the effect of clioquinol upon the resolubilization of A β from AD-affected brain. In this study, the brain specimen (from a different case than that of FIG. 2) was homogenized by the modified method of Kuo and colleagues, as described in Example 2, above. In this case a dose-dependent response to clioquinol was observed. Synthetic peptide standards that were used to calibrate densitometric quantification are shown in the two right-most lanes.

Figure 3B is a chart showing densitometry performed upon the results in FIG. 3A, above. Proportional change in the amount of A β recovered in the extraction of A β by clioquinol from human brain is shown. As little as a 1% dilution of clioquinol in PBS (100% = .8 μ M) or 8nM clioquinol is capable of doubling the recovery of A β in the soluble phase.

In sequential extraction experiments, as described above, clioquinol (1.12 μ M) has been shown to result in a 2.5 fold increase in solubilization of

A β relative to PBS alone (see Figures 3A and 3B). Significantly, the findings of the present invention show that very low (8nM) concentrations of clioquinol may resolubilize more than twice the amount of A β compared to PBS buffer alone (see Figures 3A and 3B). This suggests that such low concentrations are reasonably expected to be therapeutically effective in treating amyloidosis, preferably that occurring in AD-affected human subjects.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

All patents and publications cited in the present specification are incorporated by reference herein in their entirety.

What Is Claimed Is:

1. A method for the therapy of amyloidosis comprising administering to a patient in need thereof an effective amount of clioquinol.
2. The method of claim 1, wherein the amyloidosis therapy is therapy for Alzheimer's Disease.
3. The method of claim 2, further comprising administering to said patient Vitamin B12 supplement.
4. The method of claim 2, wherein clioquinol is administered intermittently.
5. The method of claim 2, wherein the clioquinol is administered orally.
6. The method of claim 3, wherein the Vitamin B12 is administered orally.
7. The method of claim 3, wherein Vitamin B12 is administered intramuscularly.
8. The method of claim 2, further comprising administering trace metals with or subsequent to the administration of the clioquinol.
9. The method of claim 2, wherein clioquinol is administered parenterally.
10. The method of claim 2, wherein clioquinol is administered intradermally.
11. The method of claim 2, wherein the therapy is carried out up to 10 years.

Abstract

Use of Clioquinol for the Therapy of Alzheimer's Disease

The invention relates to the identification of clioquinol as a pharmaceutically therapeutic agent for treatment of Alzheimer's disease and related pathological conditions.

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short.app

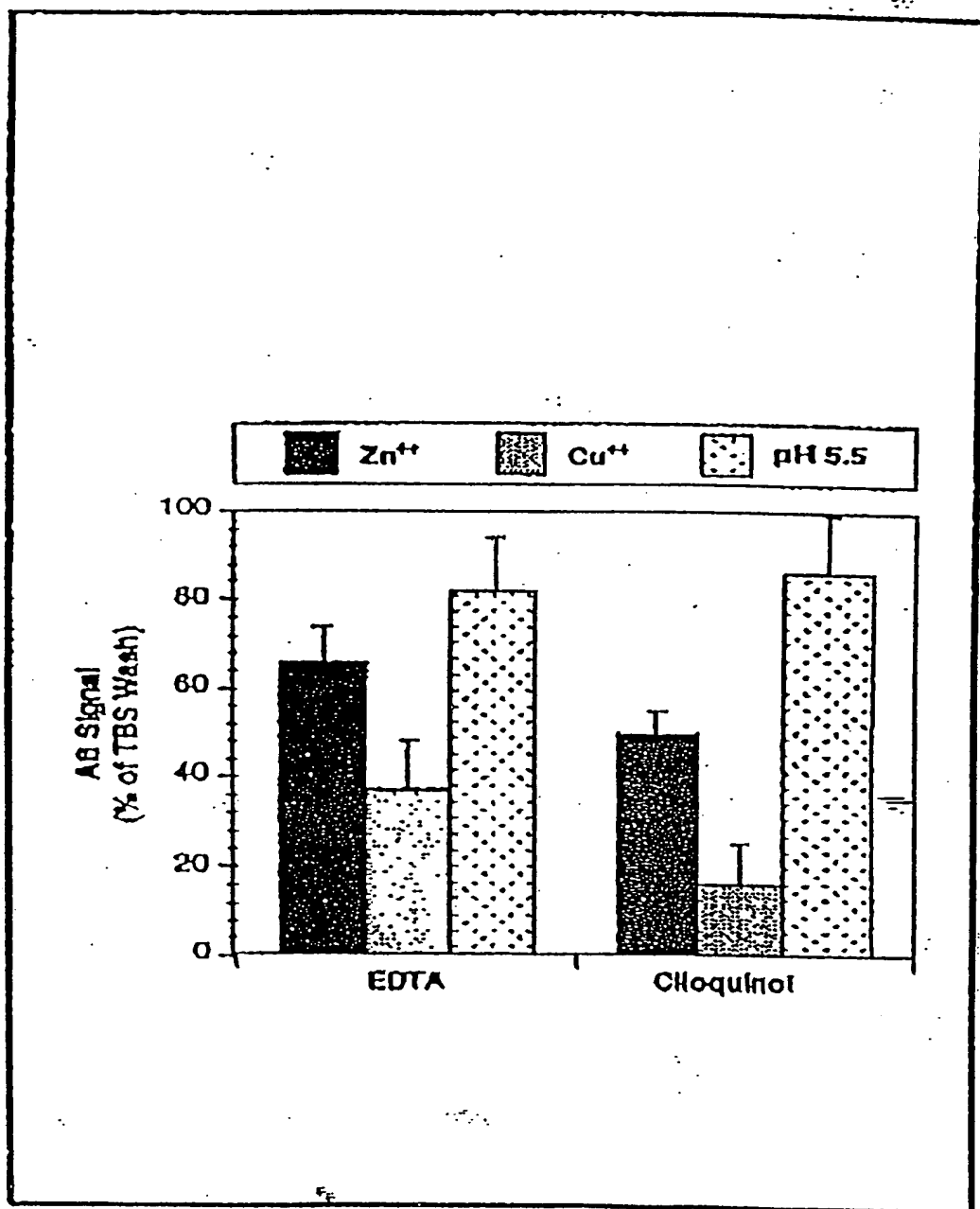
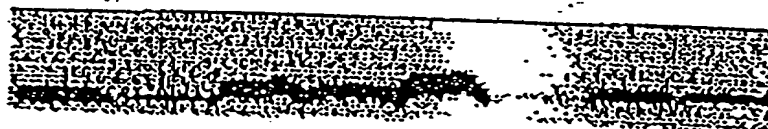
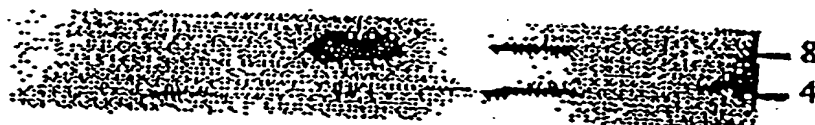


Fig. 1

Brain specimen #1



Brain specimen #2



S1 S2 S1 S2 S1 S2 S1 S2

Dilution

0

100%

10%

1%

Fig. 2

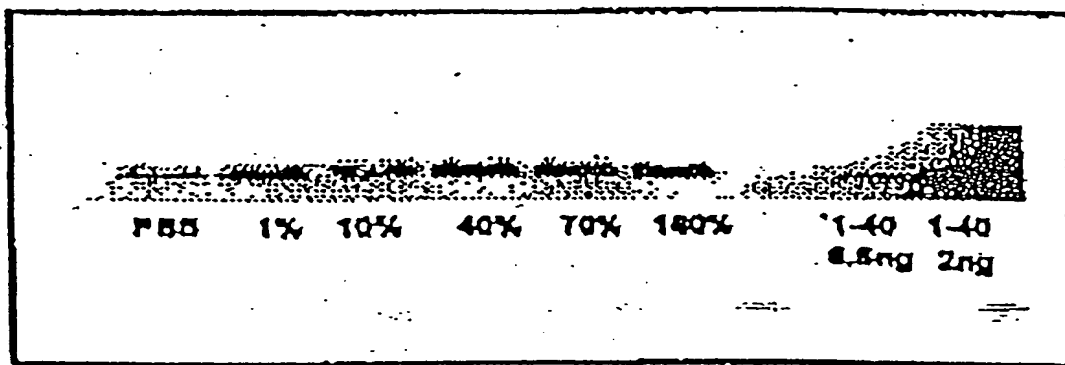


Fig. 3A

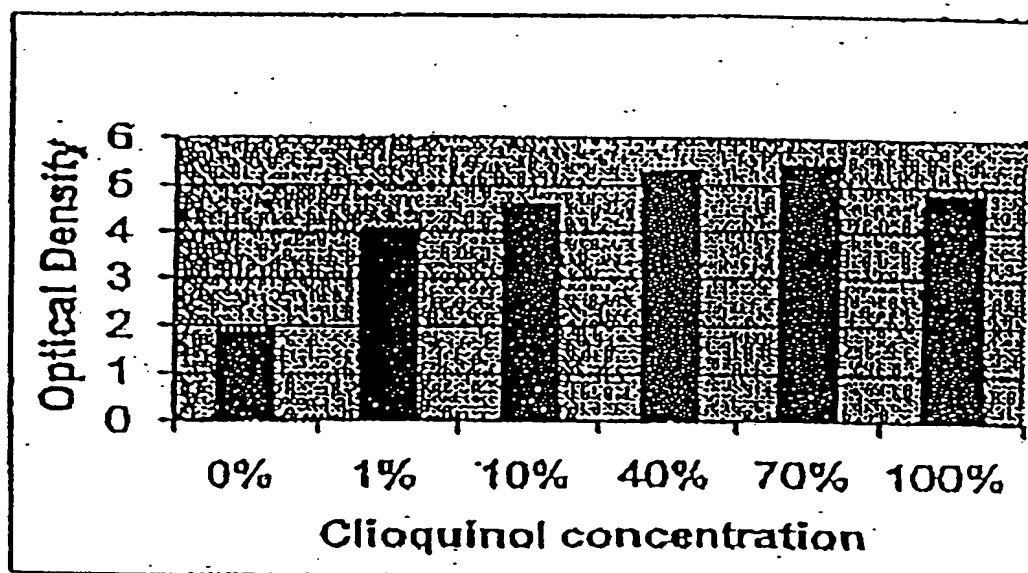


Fig. 3B

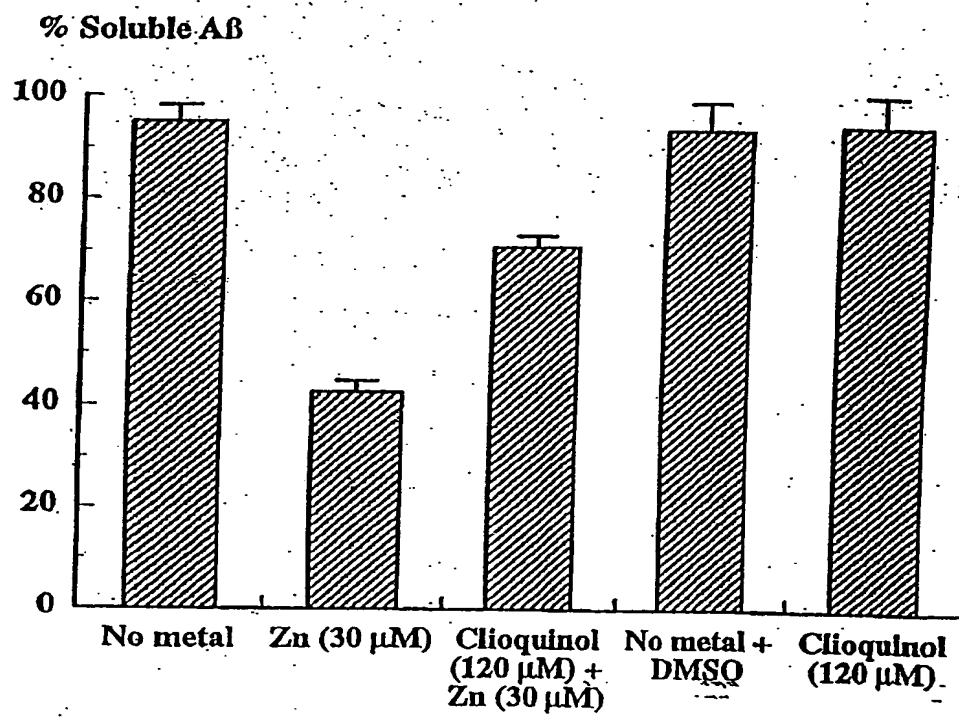


Fig. 4

Exhibit C

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

BUSH *et al.*

Appl. No. (to be assigned) (continuation of
Appl. No. 09/560,887)

Filed: October 10, 2001

For: Use of Clioquinol for the Therapy
of Alzheimer's Disease

Confirmation No.: (to be assigned)

Art Unit: (to be assigned)

Examiner: (to be assigned)

Atty. Docket: 0609.4540003/JAG/HLK

Preliminary Amendment

Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination, kindly amend the above-captioned application as follows.

This Amendment is provided in the following format:

- (A) A clean version of each replacement paragraph/section/claim along with clear instructions for entry;
- (B) Starting on a separate page, appropriate remarks and arguments. 37 C.F.R. § 1.111 and MPEP 714; and
- (C) Starting on a separate page, a marked-up version entitled: "Version with markings to show changes made."

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

Amendment

In the Specification:

At page 1, line 2, before "Background of the Invention" please insert

--Cross-Reference to Related Applications

This application is a continuation of Application No. 09/560,887, filed April 28, 2000, which is a continuation of Application No. 09/224,953, filed on January 4, 1999, now abandoned, which is a continuation of Application No. 09/032,777, filed on March 6, 1998, now abandoned. Each of these applications is herein incorporated by reference.--

In the Claims:

Please amend the claims as follows.

Please substitute the following claims 3-5 for currently pending claims 3-5:

3. (Once amended) The method of claim 1, further comprising administering to said patient Vitamin B12.

4. (Once amended) The method of claim 1, wherein the clioquinol is administered intermittently.

5. (Once amended) The method of claim 1, wherein the clioquinol is administered orally.

Please substitute the following claims 8-11 for currently pending claims 8-11:

8. (Once amended) The method of claim 1, further comprising administering trace metals with or subsequent to the administration of the clioquinol.

9. (Once amended) The method of claim 1, wherein the clioquinol is administered parenterally.

10. (Once amended) The method of claim 1, wherein the clioquinol is administered intradermally.

11. (Once amended) The method of claim 1, wherein the therapy is carried out up to 10 years.

Cancel claim 2 without prejudice or disclaimer.

Add new claims 12-46:

--12. A method of treating a subject having or suspected of having Alzheimer's disease comprising administering to the subject an amount of clioquinol effective to treat Alzheimer's disease.

13. The method according to claim 12, wherein the clioquinol is (a) administered for one to 21 days, followed by (b) a period of one to four weeks during which clioquinol is not administered.

14. A method of treating a subject having or suspected of having Alzheimer's disease comprising administering to the subject an amount of clioquinol effective to increase the solubility of amyloid-beta in the cerebrospinal fluid of said subject.

15. A method of treating a subject having or suspected of having Alzheimer's disease comprising administering to the subject (a) an amount of clioquinol effective to treat or prevent Alzheimer's disease, and (b) an amount of vitamin B₁₂.

16. The method according to claim 15 wherein the amount of vitamin B₁₂ is effective to inhibit a detrimental side effect of clioquinol administration.

17. The method according to claim 15 wherein a pharmaceutical composition comprising clioquinol is administered for one to 21 days, followed by a period of one to four weeks during which a pharmaceutical composition comprising vitamin B₁₂ is administered and clioquinol is not administered.

18. The method according to claim 15 wherein the clioquinol and vitamin B₁₂ are administered sequentially.

19. The method according to claim 15 wherein the clioquinol and vitamin B₁₂ are administered substantially simultaneously.

20. The method according to claim 16 wherein a pharmaceutical composition comprising clioquinol is administered for one to 21 days, followed by a period of one to four weeks during which a pharmaceutical composition comprising vitamin B₁₂ is administered and clioquinol is not administered.

21. The method according to claim 12, 14 or 15, wherein the subject is human.

22. The method according to claim 12 or 15, wherein the clioquinol is administered in an amount of 5-10 mg/kg body weight one to four times daily.

23. The method according to claim 12, wherein trace metals are administered together with or subsequent to the administration of clioquinol.
24. The method according to claim 12 or 15, wherein the clioquinol is administered intermittently.
25. The method according to claim 12, wherein the clioquinol is administered for up to ten years.
26. The method according to claim 12 or 15, wherein the clioquinol is formulated for oral administration.
27. The method according to claim 12 or 15, wherein the clioquinol is formulated for parenteral or intradermal administration.
28. The method according to claim 12 or 15, wherein the vitamin B₁₂ is formulated for intramuscular administration.
29. The method according to claim 12 or 15, wherein the vitamin B₁₂ is formulated for oral administration.

30. The method according to claim 15, 16 or 17, wherein the clioquinol and vitamin B₁₂ are each purified.
31. A pharmaceutical composition comprising an amount of clioquinol effective to treat Alzheimer's disease, and vitamin B₁₂.
32. The pharmaceutical composition according to claim 31, which further comprises a pharmaceutically acceptable carrier.
33. The pharmaceutical composition according to claim 31, wherein the amount of clioquinol is 5-10 mg/kg body weight.
34. The pharmaceutical composition according to claim 31, wherein the amount of vitamin B₁₂ is 7-10 mg/kg bodyweight.
35. The pharmaceutical composition according to claim 31, wherein the amount of vitamin B₁₂ is 70-100 µg/kg bodyweight.
36. The pharmaceutical composition according to claim 31, wherein the composition is formulated for parenteral or intradermal administration.

37. The pharmaceutical composition according to claim 31, wherein the composition is formulated for oral administration.
38. The pharmaceutical composition according to claim 31 or 32, wherein the clioquinol and vitamin B₁₂ are each purified.
39. A pharmaceutical composition comprising a therapeutically effective amount of clioquinol and vitamin B₁₂.
40. The pharmaceutical composition according to claim 39, which further comprises a pharmaceutically acceptable carrier.
41. The pharmaceutical composition according to claim 39, wherein the amount of clioquinol is 5-10 mg/kg body weight.
42. The pharmaceutical composition according to claim 39, wherein the amount of vitamin B₁₂ is 7-10 mg/kg bodyweight.
43. The pharmaceutical composition according to claim 39, wherein the amount of vitamin B₁₂ is 70-100 µg/kg bodyweight.

44. The pharmaceutical composition according to claim 39, wherein the composition is formulated for parenteral or intradermal administration.

45. The pharmaceutical composition according to claim 39, wherein the composition is formulated for oral administration.

46. The pharmaceutical composition according to claim 39 or 40, wherein the clioquinol and vitamin B₁₂ are each purified.--

Remarks

Prompt and favorable consideration of this Preliminary Amendment is respectfully requested. Claim 2 has been canceled, and claims 12-46 have been added. Upon entry of the foregoing Preliminary Amendment, claims 1 and 3-46 will be subject to examination in the application, with claims 1, 12, 14, 15, 31 and 39 being the independent claims.

Applicants have amended the specification to cross-reference related Application Nos. 09/560,887, 09/224,953 and 09/032,777.

In addition, the application has been amended to add new claims 12-46. These claims were added in the parent application to copy claims from issued U.S. patents. More specifically, new claims 12-27 and 29-30 correspond to claims 1-6, 8-14, 16-19, 22-31 and 38 of U.S. Patent No. 6,001,852, issued on December 14, 1999; and new claims 31-46 correspond to claims 1-9 and 16 of U.S. Patent No. 5,994,323, issued on November 30, 1999; and to claims 21-29 and 36 of U.S. Patent No. 5,980,914, issued on November 9, 1999.

Support for claims 12-46 can be found, *inter alia*, as described in the following table:

Claim	Location of Support in Specification
12	page 1, lines 7-16; page 5, line 21 to page 6, line 20; page 7, lines 24-25; page 18, lines 4-6; page 19, lines 5-6
13	page 3, lines 23-25 and 27-29; page 5, lines 17-20; page 9, lines 3-12.
14	page 6, lines 1-20; page 16, line 14 to page 18, line 6.

Claim	Location of Support in Specification
15	page 3, lines 9-12 and 26-27; page 8, lines 20-26; page 9, lines 1-2 and 11-12; page 19, lines 7-8.
16	page 8, lines 20-26.
17	page 3, lines 23-25 and 27-29; page 5, lines 17-20; page 9, lines 3-12.
18 & 19	page 3, lines 23-25.
20	page 3, lines 23-25 and 27-29; page 5, lines 17-20; page 9, lines 3-12.
21	page 12, line 29 to page 13, line 2; page 18, lines 4-6.
22	page 3, lines 13-15; page 8, lines 6-12, 18-19 and 27-28; page 12, lines 17-19.
23	page 3, lines 11-12 and 22-27; page 19, lines 17-19.
24	page 3, lines 27-29; page 19, lines 17-19.
25	page 4, lines 1-2; page 19, lines 24-25.
26	page 3, lines 26-27; page 10, line 22 to page 11, line 22; page 19, lines 11-12.
27	page 3, lines 26-27; page 12, lines 1-11; page 19, lines 20-22.
28	page 3, lines 16-21; page 19, lines 15-16.
29	page 3, lines 16-21 and 26-27; page 19, lines 13-14.
30	page 11, lines 19-21.
31	page 3, lines 11-12 and 23-25; page 8, lines 23-26; page 9, line 17 to page 12, line 28; page 12, lines 21-23.
32	page 9, lines 17-19; page 10, lines 1-4; page 11, lines 7-14 and 23-26.
33	page 3, lines 13-15; page 8, lines 6-12, 18-19 and 27-28; page 12, lines 17-19.
34	page 3, lines 17-19.
35	page 3, lines 19-21.
36	page 3, lines 26-27; page 12, lines 1-11; page 19, lines 20-21.
37	page 3, lines 16-21 and 26-27; page 10, line 22 to page 11, line 22; page 19, lines 11-12 and 13-14.
38	page 11, lines 19-21.
39	page 3, lines 11-12 and 23-25; page 8, lines 23-26; page 9, line 17 to page 12, line 28; page 12, lines 21-23.
40	page 9, lines 17-19; page 10, lines 1-4; page 11, lines 7-14 and 23-26.
41	page 3, lines 13-15; page 8, lines 6-12, 18-19 and 27-28; page 12, lines 17-19.
42	page 3, lines 17-19.
43	page 3, lines 19-21.

Claim	Location of Support in Specification
44	page 3, lines 26-27; page 12, lines 1-11; page 19, lines 20-22.
45	page 3, lines 16-21 and 26-27; page 10, line 22 to page 11, line 22; page 19, lines 11-14.
46	page 11, lines 19-21.

These changes are believed to introduce no new matter, and their entry is respectfully requested.

Summary

Applicants believe that this application is now in condition for examination. Early notice to this effect is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Heidi Kraus *12/9/01*

Heidi L. Kraus
Attorney for Applicant
Registration No. 43,730

Date: 10-10-01

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600

JAG/HLK

Version with markings to show changes made

In the Claims:

The following claims 3-5 have been substituted for currently pending claims 3-5:

3. (Once amended) The method of claim [2] 1, further comprising administering to said patient Vitamin B12 [supplement].

4. (Once amended) The method of claim [2] 1, wherein the clioquinol is administered intermittently.

5. (Once amended) The method of claim [2] 1, wherein the clioquinol is administered orally.

The following claims 8-11 have been substituted for currently pending claims 8-11:

8. (Once amended) The method of claim [2] 1, further comprising administering trace metals with or subsequent to the administration of the clioquinol.

9. (Once amended) The method of claim [2] 1, wherein the clioquinol is administered [parenterally] parenterally.

10. (Once amended) The method of claim [2] 1, wherein the clioquinol is administered
[intradermally] intradermally.

11. (Once amended) The method of claim [2] 1, wherein the therapy is carried out up
to 10 years.

Claim 2 has been canceled.

Claims 12-46 have been added.

Exhibit D

Declaration for Patent Application

Docket Number: 0609.4540003/JAG/FRC

As a below named inventor, I hereby declare that:

My residence, mailing address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter that is claimed and for which a patent is sought on the invention entitled: Use of Clioquinol for the Therapy of Alzheimer's Disease.

the specification of which is attached hereto unless the following box is checked:

- ☒ was filed on October 10, 2001;
as United States Application Number 09/972,913; and
was amended on October 10, 2001 (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information that is material to patentability as defined in 37 C.F.R. § 1.56, including for continuation-in-part applications, material information that became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or (f), or § 365(b) of any foreign application(s) for patent, inventor's or plant breeder's rights certificate(s), or § 365(a) of any PCT international application, which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent, inventor's or plant breeder's rights certificate(s), or PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Claimed

(Application No.)

(Country)

(Day/Month/Year Filed)

☐ Yes ☐ No

(Application No.)

(Country)

(Day/Month/Year Filed)

☐ Yes ☐ No

Send Correspondence to:

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.
1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934

Direct Telephone Calls to:

(202) 371-2600

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor	Ashley I. Bush	
Signature of sole or first inventor		Date
Residence	Sommerville, MA	
Citizenship	Australia	
Mailing Address	91 Summer Street, Apt. 3 Sommerville, MA 02143	
Full name of second inventor	Rudolph E. Tanzi	
Signature of second inventor		Date
Residence	Hull, MA	
Citizenship	USA	
Mailing Address	3 Oceanside Hull, MA 02045	
Full name of third inventor	Mikhal Xilinas	
Signature of third inventor	✓	✓ Date
Residence	Athens, Greece	
Citizenship	Greece	
Mailing Address	15 Atalante 145 63 Kisifia, Greece	

Full name of fourth inventor	Robert Cherny
Signature of fourth inventor	Date
Residence	Melbourne, Australia
Citizenship	Australia
Mailing Address	33 Davey Avenue Brighton East, Victoria Australia

P:\USERS\pdomally\Frank.C\0609\4540003\Declaration
SKGF Rev. 5/16/01 mac

(Supply similar information and signature for subsequent joint inventors, if any)

Exhibit E

**37 C.F.R. § 10.18(b) and (c): Effect of Signature and Certificate
for Correspondence Filed in the Patent and Trademark Office**

37 C.F.R. § 10.18(b): By presenting to the Office, (whether by signing, filing, submitting, or later advocating), any paper, the party presenting such paper, whether a practitioner or non-practitioner, is certifying that --

- (1) All statements made therein of the party's own knowledge are true, all statements made therein on information and belief are believed to be true, and all statements made therein are made with the knowledge that whoever, in any matter within the jurisdiction of the USPTO, knowingly and willfully falsifies, conceals, or covers up by any trick, scheme, or device a material fact, or makes any false, fictitious or fraudulent statements or representations, or makes or uses any false writing or document knowing the same to contain any false, fictitious or fraudulent statement or entry, shall be subject to the penalties set forth under 18 U.S.C. § 1001, and that violations of this paragraph may jeopardize the validity of the application or document, or the validity or enforceability of any patent, trademark registration, or certificate resulting therefrom; and
- (2) To the best of the party's knowledge, information and belief, formed after an inquiry reasonable under the circumstances, that:
 - (i) The paper is not being presented for any improper purpose, such as to harass someone or to cause unnecessary delay or needless increase in the cost of prosecution before the Office;
 - (ii) The claims and other legal contentions therein are warranted by existing law or by a nonfrivolous argument for the extension, modification, or reversal of existing law or the establishment of new law;
 - (iii) The allegations and other factual contentions have evidentiary support or, if specifically so identified, are likely to have evidentiary support after a reasonable opportunity for further investigation or discovery; and
 - (iv) The denials of factual contentions are warranted on the evidence, or if specifically so identified, are reasonably based on a lack of information or belief.

37 C.F.R. § 10.18(c): Violations of paragraph (b)(1), by a practitioner or a non-practitioner, may jeopardize the validity of the application or document, or the validity or enforceability of any patent, trademark registration, or certificate resulting therefrom. Violations of any of paragraphs (b)(2)(i) through (iv) of this section are, after notice and reasonable opportunity to respond, subject to such sanctions as deemed appropriate by the Commissioner, or the Commissioner's designee, which may include, but are not limited to, any combination of:

- (1) Holding certain facts to have been established;
- (2) Returning papers;
- (3) Precluding a party from filing a paper, or presenting or contesting an issue;
- (4) Imposing a monetary sanction;
- (5) Requiring a terminal disclaimer for the period of the delay; or
- (6) Terminating the proceedings in the Patent and Trademark Office.

Exhibit F

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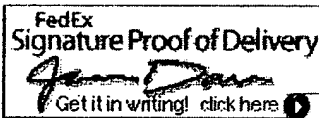
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Package statusATHENS GR	07/28/2002 14:58	Package available for clearance
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Exhibit G

From: xilinas <xilinas@compulink.gr>
T : <frankc@skgf.com>
Date: 8/8/02 7:27AM

Dear Mr. Cottingham,

thank you for your letter of 25 July 2002. I am sending to Mr. Georgopoulos, who will be my lawyer, your documents for advice. Unfortunately Mr. Georgopoulos' Law Office is closed for the August vacations.

I would like to inform you that there are ongoing negotiations between PN Gerolymatos and Prana to resolve the legal differences between them. Therefore personally I think that the outcome of this negotiation will facilitate the clioquinol development and resolve the running difficulties.

I would also like to inform you that I am French citizen and my correct name is Michel Xilinas, resident of Larmaca, Cyprus and not "Mikhal et c..").

In Kifisia Greece where my daughters are living you can continue sending any correspondance (c/o Chloe Xilinas, 15a Atalante, 145 63 Kifisia, Greece). Since I am on travel most of the time my daughters follow-up my mail regularly. You can reach me on my mobile telephone +30 944 42 81 79 most of the time.

Mr. Georgopoulos has a mobile telephone in his vacation place where you can reach him for urgent matters (+30 944 77 16 72).

Kind regards

Michel Xilinas, MD, DSc

CC: "dgeorgopoulos@otenet.gr" <dgeorgopoulos@otenet.com>

Exhibit H

From: xilinas <xilinas@compulink.gr>
To: <frankc@skgf.com>
Date: 9/6/02 1:17PM
Subject: Fw:

Dear Mr. Cottingham,
pls find attached the letter that Mr. Georgopoulos has addressed to you,
kind regards
Michel Xilinas

— Original Message —

From: xilinas
To: frankc@skgf.com
Cc: dgeorgopoulos@otenet.gr
Sent: Thursday, August 08, 2002 2:26 PM

Dear Mr. Cottingham,
thank you for your letter of 25 July 2002. I am sending to Mr. Georgopoulos, who will be my lawyer, your documents for advice. Unfortunately Mr. Georgopoulos' Law Office is closed for the August vacations.
I would like to inform you that there are ongoing negotiations between PN Gerolymatos and Prana to resolve the legal differences between them. Therefore personally I think that the outcome of this negotiation will facilitate the clioquinol development and resolve the running difficulties.
I would also like to inform you that I am French citizen and my correct name is Michel Xilinas, resident of Larnaca, Cyprus and not "Mikhal et c..").
In Kifisia Greece where my daughters are living you can continue sending any correspondence (c/o Chloe Xilinas, 15a Atalante, 145 63 Kifisia, Greece). Since I am on travel most of the time my daughters follow-up my mail regularly. You can reach me on my mobile telephone +30 944 42 81 79 most of the time.
Mr. Georgopoulos has a mobile telephone in his vacation place where you can reach him for urgent matters (+30 944 77 16 72).
Kind regards
Michel Xilinas, MD, DSc

Dear Mr Cottingham,

Dr. Michel Xilinas has instructed me as his lawyer and legal advisor and gave to me your letter and documents ref. 0609 454 0003/JAG/FRC, dated July 25th, 2002.

It is a fact that Dr. Xilinas has conceived first and participated in the inventions related to the use of clioquinol in Alzheimer's and related diseases.

Before I can evaluate the situation and advise Dr Xilinas in relation to your aforementioned request for signature, I kindly ask you to provide me with the necessary background information. In particular, from what Dr. Xilinas has understood and conveyed to me, without being able to provide me with any useful details, there appears to be a pending legal case between Prana, MGH and P.N. Gerolymatos. Since this case would appear to be linked to the US utility patent Application 09/972,913, and therefore would appear to be of importance in our context, I need to have a clear picture of the situation, at your earliest convenience. I would also wish to inform you that the correct name of Dr. Xilinas is Michel (and not Michael) and that he is a French national with residence in Larnaca, Cyprus.

For all correspondance on the matter kindly use my following particulars:

Dimitri M. Georgopoulos

Advocate

45, Koniari Str.

11471 Athens

Greece

Tel. +3010-64.33.722, 6430838

Fax + 3010-6449859

e-mail: dgeorgop@otenet.gr

Sincerely yours

D.M.Georgopoulos

Lawyer

cc. Dr. M. Xilinas

Exhibit I

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

ATTORNEYS AT LAW

1100 New York Avenue, N.W.

Suite 600

Washington, D.C. 20005-3934

Facsimile Cover Sheet

urgent ☒ return reply requested ☒ original will be sent as confirmation ☐

DATE: September 10, 2002

PHONE NO.: 011- 3010- 6449859

PAGES: 23 (including this cover sheet)

TO: Mr. Dimitri M. Georgopoulos

CC: Colm Lawler, Ph.D.
Simon Tout, Ph.D.

(617) 726-1668
011 61 3 9243 8333

FROM: Frank R. Cottingham (FRC)

RE: U.S. Utility Patent Appl. No. 09/972,913; Filed: October 10, 2001

For: Use of Clioquinol for the Therapy of Alzheimer's Disease

MGH REF: 1290.3

GH REF: VS:SDT:GF35003:GM25371

OUR REF: 0609.4540003/JAG/FRC

MESSAGE

Letter along with enclosures follow.

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STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

ATTORNEYS AT LAW

1100 New York Avenue, N.W.

Suite 600

Washington, D.C. 20005-3934

Facsimile Cover Sheet

urgent ☒ return reply requested ☒ original will be sent as confirmation ☐

DATE: September 10, 2002

PHONE NO.: 011- 3010- 6449859

PAGES: 23 (including this cover sheet)

TO: Mr. Dimitri M. Georgopoulos

CC: Colm Lawler, Ph.D.

(617) 726-1668

Simon Tout, Ph.D.

011 61 3 9243 8333

FROM: Frank R. Cottingham (FRC)

RE: U.S. Utility Patent Appl. No. 09/972,913; Filed: October 10, 2001

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

PRANA BIOTECHNOLOGY, LTD.,

Level 1, 100 Dorcas Street

South Melbourne, Victoria, Australia,

THE GENERAL HOSPITAL

CORPORATION,

55 Fruit Street

Boston, Massachusetts,

ASHLEY I BUSH,

91 Summer Street, Apartment 3

Somerville, Massachusetts,

ROBERT CHERNY,

33 Davey Avenue

Brighton East, Victoria, Australia,

and RUDOLPH E. TANZI,

3 Oceanside Drive

Hull, Massachusetts,

Plaintiffs,

v.

P.N. GEROLYMATOS S.A.,

13 Asklepiou Street 145 65

Kryoneri Athens, Greece,

CASE NUMBER 1:01CV02052

JUDGE: Thomas Penfield Jackson

DECK TYPE: General Civil

DATE STAMP: 09/27/2001

and PANAYOTIS N. GEROLYMATOS,

Kryoneri Athens, Greece,

Defendants.

COMPLAINT AND JURY DEMAND

Introduction

1. This is an action to correct the inventorship of U.S. Patent Nos. 6,001,852 and 5,994,323 pursuant to 35 U.S.C. § 256. The plaintiffs also seek a declaratory judgment that at least Ashley L Bush, Robert Cherny, and Rudolph E. Tanzi are the true inventors of U.S. Patent Nos. 6,001,852 and 5,994,323; that Panayotis N. Gerolymatos is not an inventor of those patents; that Prana Biotechnology, Ltd. and The General Hospital Corporation are assignees of U.S. Patent Nos. 6,001,852 and 5,994,323; and that P.N. Gerolymatos S.A. is not an assignee of those patents. In addition, the plaintiffs seek to recover damages for conversion and unjust enrichment.

The Parties

2. The plaintiff Prana Biotechnology Ltd. ("Prana") is an Australian corporation with a principal place of business at Level 1, 100 Dorcas Street, South Melbourne, Victoria, Australia. Prana is a startup biotechnology company whose business includes research, development, and commercialization of products for the diagnosis and therapy of neurological conditions such as Alzheimer's Disease.

3. The plaintiff The General Hospital Corporation is a Massachusetts corporation doing business as Massachusetts General Hospital ("MGH"), with a principal place of business at 55 Fruit Street, Boston, Massachusetts.

4. The plaintiff Dr. Ashley L. Bush ("Dr. Bush") is an individual residing at 91 Summer Street, Apartment 3, Somerville, Massachusetts. Dr. Bush has been at all times relevant to this action and currently is an employee of MGH. Dr. Bush is a member of Prana's Scientific Advisory Board.

5. The plaintiff Dr. Robert Cherny ("Dr. Cherny") is an individual residing at 33 Davey Avenue, Brighton East, Victoria, Australia. Dr. Cherny has been at all times relevant to this action and currently is an employee of the University of Melbourne and an honorary staff member of the Mental Health Research Institute, a research affiliate of the University of Melbourne.

6. The plaintiff Dr. Rudolph E. Tanzi ("Dr. Tanzi") is an individual residing at 3 Oceanside Drive, Hull, Massachusetts. Dr. Tanzi has been at all times relevant to this action and currently is an employee of MGH. Dr. Tanzi is a member of Prana's Scientific Advisory Board.

7. The defendant P.N. Gerolymatos S.A. ("PNG") is a Greek corporation with a principal place of business at 13 Asklipiou Street 145 65, Kryoneri Athens, Greece. PNG is listed as the assignee on U.S. Patent Nos. 6,001,852 and 5,994,323. Upon information and belief, PNG has not designated any person residing within the United States on whom may be served process or notice of proceedings affecting U.S. Patent Nos. 6,001,852 and 5,994,323 or rights thereunder.

8. The defendant Mr. Panayotis N. Gerolymatos ("Mr. Gerolymatos") is an individual residing, upon information and belief, in Kryoneri Athens, Greece. Mr. Gerolymatos currently is and, upon information and belief, has been at all times relevant to this action, President, Chief Executive Officer, and Chairman of the Board of Directors of PNG.

Jurisdiction and Venue

9. This Court has subject matter jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331, 1338, 1367 and 2201, and 35 U.S.C. § 256.
10. This Court has personal jurisdiction over the defendants pursuant to 35 U.S.C. § 293.
11. Venue is proper in this judicial district pursuant to 28 U.S.C. § 1391(d) and 35 U.S.C. § 293.

Facts

12. U.S. Patent No. 6,001,852 ("the '852 patent") (attached as Exh. A), entitled "Clioquinol for the Treatment of Alzheimer's Disease," issued on December 14, 1999. The '852 patent is directed to the use of clioquinol, a zinc chelating agent, for the treatment of Alzheimer's Disease.
13. Mr. Gerolymatos is named as the sole inventor and PNG as the assignee of the '852 patent.
14. U.S. Patent No. 5,994,323 ("the '323 patent") (attached as Exh. B), entitled "Pharmaceutical Compositions Comprising Clioquinol in Combination with Vitamin B12 and ... Therapeutic and Prophylactic Uses Thereof," issued on November 30, 1999. The '323 patent is directed to pharmaceutical compositions comprising clioquinol and vitamin B12, and methods of using clioquinol in combination with vitamin B12 for the treatment of conditions including Alzheimer's Disease.
15. Mr. Gerolymatos is named as the sole inventor and PNG as the assignee of the '323 patent.
16. In fact, at least Drs. Bush, Cherny, and Tanzi conceived and reduced to practice the invention claimed by the '852 and '323 patents, namely the use of clioquinol to treat

Alzheimer's Disease, preferably in combination with vitamin B12 to reduce side effects. Mr. Gerolymatos did not participate in the conception or reduction to practice of this invention.

17. Dr. Mikhal Xilinas ("Dr. Xilinas") is an individual residing, upon information and belief, in Athens, Greece. Upon information and belief, Dr. Xilinas also may be an inventor of the invention claimed in the '852 and '323 patents. Upon information and belief, Dr. Xilinas has, at different times, both claimed and denied that he is an inventor of the subject matter claimed in the '852 and '323 patents.

18. MGH has filed a U.S. patent application, serial number 09/560,887 ("the MGH application"), directed to the use of clioquinol for the treatment of Alzheimer's Disease, naming as the inventors Drs. Bush, Cherny, Tanzi, and Xilinas.

19. Upon information and belief, Mr. Gerolymatos derived the invention claimed by the '852 and '323 patents from and/or through Drs. Bush, Cherny, Tanzi, and Xilinas. Mr. Gerolymatos then filed multiple patent applications directed to the use of clioquinol for the treatment of Alzheimer's Disease, including the U.S. patent applications that issued as the '852 and '323 patents. The applications name Mr. Gerolymatos as the sole inventor and PNG as the assignee.

20. Drs. Bush, Cherny, and Tanzi did not consent to the filing of Mr. Gerolymatos' patent applications. Mr. Gerolymatos denied Dr. Bush's repeated requests to be named as an inventor on any patent application that might be filed on the use of clioquinol for the treatment of Alzheimer's Disease.

21. As a result of their employment agreements, Drs. Bush and Tanzi have been at all times relevant to this action and currently are under an obligation to assign to MGH any patent applications on which they are named as inventors. Similarly, as a result of his employment

agreement, Dr. Cherny has been at all times relevant to this action and currently is under an obligation to assign to the University of Melbourne any patent application on which he is named as an inventor.

22. Prana is the assignee of the University of Melbourne's interest in any patent or application directed to the inventions of Dr. Cherny that are disclosed in the '852 and '323 patents. Prana is the exclusive licensee of MGH's interest in any patent or application directed to the inventions of Drs. Bush and Tanzi that are disclosed in the '852 and '323 patents.

23. The defendants have developed and capitalized on a drug program for the use of clioquinol in Alzheimer's Disease without fairly compensating the plaintiffs for the use of their invention. For example, upon information and belief, the defendants and the Danish pharmaceutical company H. Lundbeck A/S have entered into a marketing agreement for clioquinol in Alzheimer's Disease, the proceeds of which will not be shared with the plaintiffs. The '852 and '323 patents and corresponding international patents and applications have substantially furthered the defendants' ability to develop and fund their drug program for clioquinol in Alzheimer's Disease.

24. The '852 and '323 patents, the defendants' corresponding foreign patents and applications, and the defendants' competing drug program have substantially hindered Prana's ability to obtain funding for its research regarding the use of clioquinol in Alzheimer's Disease, and to commercialize on its own promising drug program. These impediments have been especially harmful to Prana as a startup biotechnology company seeking to establish itself in a competitive pharmaceutical market.

Count I - Correction of Inventorship Under 35 U.S.C. § 256

25. The plaintiffs repeat the allegations of paragraphs 1-24 as if set forth here in full.

26. At least Drs. Bush, Cherny, and Tanzi are the true inventors of the inventions claimed in the '852 and '323 patents.

27. Without any deceptive intention on their part, Drs. Bush, Cherny, and Tanzi were not named as inventors on the '852 and '323 patents.

28. Mr. Gerolymatos is the sole inventor named on the '852 and '323 patents.

29. Mr. Gerolymatos is not an inventor of the inventions claimed in the '852 and '323 patents.

30. Pursuant to § 256, at least Drs. Bush, Cherny, and Tanzi should be substituted as named inventors of the '852 and '323 patents, and Mr. Gerolymatos should be removed as the named inventor of those patents.

Count II – Declaratory Judgment

31. The plaintiffs repeat the allegations of paragraphs 1-30 as if set forth here in full.

32. Drs. Bush, Cherny, and Tanzi are entitled to a declaratory judgment that they, at least, are the true inventors of the '852 and '323 patents, and that Mr. Gerolymatos is not an inventor of those patents.

33. MGH, as the assignee of Drs. Bush and Tanzi, and Prana, as the assignee of the University of Melbourne, which is the assignee of Dr. Cherny, are entitled to a declaratory judgment that they are assignees of the '852 and '323 patents, and that PNG is not an assignee of those patents.

Count III – Conversion

34. The plaintiffs repeat the allegations of paragraphs 1-33 as if set forth here in full.

35. The defendants have knowingly and wrongfully assumed and exercised dominion and control over the plaintiffs' property in a manner inconsistent with and substantially interfering with the plaintiffs' rights.

36. The plaintiffs have sustained substantial damages arising from the defendants' conversion.

Count IV – Unjust Enrichment

37. The plaintiffs repeat the allegations of paragraphs 1-36 as if set forth here in full.

38. The defendants have received benefits at the plaintiff's expense and have appreciated the benefits.

39. The defendants have accepted and retained the benefits under circumstances that make it unjust for the defendants to retain the benefits without paying the plaintiffs the value thereof.

40. The plaintiffs have sustained damages as a result of the defendants' unjust enrichment.

WHEREFORE, the plaintiffs request that the Court:

1. Issue an order directing the Commissioner for Patents to issue a certificate correcting the inventorship of U.S. Patent Nos. 6,001,852 and 5,994,323;
2. Issue a declaration adjudging that:
 - (a) At least Ashley I. Bush, Robert Cherny, and Rudolph E. Tanzi are the true inventors of U.S. Patent Nos. 6,001,852 and 5,994,323;
 - (b) Panayotis N. Gerolymatos is not an inventor of those patents;
 - (c) Prana Biotechnology, Ltd. and The General Hospital Corporation are assignees of U.S. Patent Nos. 6,001,852 and 5,994,323 ; and
 - (d) P.N. Gerolymatos S.A. is not an assignee of those patents;
3. Award the plaintiffs compensatory damages;
4. Award the plaintiffs their costs and attorneys' fees; and

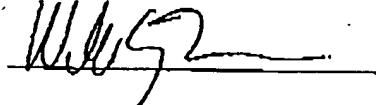
5. Award the plaintiffs such further relief as the Court may deem just and proper.

Jury Demand

The plaintiffs hereby demand a trial by jury for any and all issues so triable.

PRANA BIOTECHNOLOGY, LTD.,
THE GENERAL HOSPITAL
CORPORATION, ASHLEY I. BUSH,
ROBERT CHERNY, and RUDOLPH E.
TANZI,

By their attorneys,



William G. McElwain
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August 31, 2001

Of Counsel

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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

PRANA BIOTECHNOLOGY, LTD.,
Level 1, 100 Dorcas Street
South Melbourne, Victoria, Australia

THE GENERAL HOSPITAL
CORPORATION,
55 Fruit Street
Boston, Massachusetts

ASHLEY I. BUSH,
91 Summer Street, Apartment 3
Somerville, Massachusetts

ROBERT CHERNY
33 Davey Avenue
Brighton East, Victoria, Australia

and RUDOLPH E. TANZI,
3 Oceanside Drive
Hull, Massachusetts

Plaintiffs,

-v-

P.N. GEROLYMATOS S.A.
13 Asklepiou Street
145 65 Kryoneri Attika, Greece

and PANAYOTIS N. GEROLYMATOS,
13 Asklepiou Street
145 65 Kryoneri Attika, Greece

Defendants.

Civil Action No. 1:01CV02052 TPJ

AMENDED ANSWER AND
COUNTERCLAIMS

Defendants, P.N. Gerolymatos S.A. (hereinafter "Gerolymatos S.A.") and Panayotis N.

Gerolymatos (hereinafter "Gerolymatos"), hereby answer the Complaint of Plaintiffs, Prana

Biotechnology, Ltd. (hereinafter "Prana"). The General Hospital Corporation (hereinafter "MGH," since it allegedly does business as Massachusetts General Hospital), Ashley I. Bush (hereinafter "Bush"), Robert Cherny (hereinafter "Cherny"), and Rudolph E. Tanzi (hereinafter "Tanzi"), as follows:

1. Defendants deny any implicit allegation that Plaintiffs are entitled to the declaratory judgments or damages they seek. Defendants admit all of the remaining allegations of paragraph 1 of the Complaint.

2. Upon information and belief, Defendants admit that Prana is an Australian Corporation with a principal place of business at Level 1, 100 Dorcas Street, South Melbourne, Victoria, Australia, and that Prana is a start-up biotechnology company. Defendants lack sufficient information to form a belief as to the truth of the remaining allegations of paragraph 2 of the Complaint and therefore deny same.

3. Upon information and belief, Defendants admit the allegations of paragraph 3 of the Complaint.

4. Upon information and belief, Defendants admit that Bush is an individual residing at 91 Summer Street, Apt. 3, Somerville, Massachusetts. Defendants lack sufficient information to form a belief as to the truth of the remaining allegations of paragraph 4 of the Complaint and therefore deny same.

5. Upon information and belief, Defendants admit that Cherny is an individual residing at 33 Davey Avenue, Brighton East, Victoria, Australia. Defendants lack sufficient information to form a belief as to the truth of the remaining allegations of paragraph 5 of the Complaint and therefore deny same.

6. Upon information and belief, Defendants admit that Tanzi is an individual residing at 3 Oceanside Drive, Hull, Massachusetts. Defendants lack sufficient information to form a belief as to the truth of the remaining allegations of paragraph 6 of the Complaint and therefore deny same.

7. Defendants admit the allegations of paragraph 7 of the Complaint.

8. Defendants admit the allegations of paragraph 8 of the Complaint.

9. Defendants admit that this Court has subject matter jurisdiction over Counts I and II of the Complaint pursuant to 28 U.S.C. §§1331 and/or 1338. Defendants deny all of the remaining allegations of paragraph 9 of the Complaint.

10. Defendants admit that this Court has personal jurisdiction over Gerolymatos S.A. Defendants deny all of the remaining allegations of paragraph 10 of the Complaint.

11. Defendants admit the allegations of paragraph 11 of the Complaint.

12. Defendants admit that U.S. Patent No. 6,001,852 ("the '852 patent") is entitled "Clioquinol for the Treatment of Alzheimer's Disease," and that such patent issued on December 14, 1999. Defendants further admit that the patent is directed to, *inter alia*, the use of clioquinol for the treatment of Alzheimer's Disease, and that clioquinol is a zinc chelating agent. Defendants deny all of the remaining allegations of paragraph 12 of the Complaint.

13. Defendants admit the allegations of paragraph 13 of the Complaint.

14. Defendants admit that U.S. Patent No. 5,994,323 ("the '323 patent") is entitled "Pharmaceutical Compositions Comprising Clioquinol in Combination with Vitamin B12 and Therapeutic and Prophylactic Uses Thereof," and that such patent issued on November 30, 1999. Defendants further admit that the patent is directed to, *inter alia*, pharmaceutical compositions

comprising clioquinol and vitamin B12, and methods of using clioquinol in combination with vitamin B12 for the treatment of conditions including Alzheimer's Disease. Defendants deny all of the remaining allegations of paragraph 14 of the Complaint.

15. Defendants admit the allegations of paragraph 15 of the Complaint.

16. Defendants deny the allegations of paragraph 16 of the Complaint.

17. Defendants admit the allegations of paragraph 17 of the Complaint that Dr. Mikhal Xilinas ("Xilinas") is an individual residing in Athens, Greece, and that he has, at different times, both claimed and denied that he is an inventor of the subject matter claimed in the '852 and '323 patents. The statement in paragraph 17 of the Complaint that "[u]pon information and belief, Dr. Xilinas also may be an inventor of the invention claimed in the '852 and '323 patents" is neither an allegation that Dr. Xilinas is an inventor nor an allegation that Dr. Xilinas is not an inventor of the subject matter claimed in said patents, and therefore is not an allegation that Defendants can properly admit or deny.

18. Defendants lack sufficient information to form a belief as to the truth of the allegations of paragraph 18 of the Complaint and therefore deny same.

19. Defendants admit that Gerolymatos S.A. filed multiple patent applications directed to *inter alia*, the use of clioquinol for the treatment of Alzheimer's Disease, including the U.S. patent applications that issued as the '852 and '323 patents. Defendants further admit that said applications name Gerolymatos as the sole inventor and Gerolymatos S.A. as the assignee. Defendants deny all of the remaining allegations of paragraph 19 of the Complaint.

20. Defendants admit that after Gerolymatos S.A. filed certain of its patent applications relating to clioquinol for the treatment of Alzheimer's Disease, Bush reversed what Defendants

had understood his position to be, and requested to be named as a co-inventor on said patent application(s). Defendants deny all of the remaining allegations of paragraph 20 of the Complaint.

21. Defendants lack sufficient information to form a belief as to the truth of the allegations of paragraph 21 of the Complaint and therefore deny same.

22. Defendants lack sufficient information to form a belief as to the truth of the allegations of paragraph 22 of the Complaint and therefore deny same.

23. Defendants admit that Gerolymatos S.A. was developing and capitalizing on a drug program for the use of clioquinol in Alzheimer's Disease, and that, although substantially hindered by the actions of Prana as alleged in the Second, Third and Fourth Counterclaims of this pleading, Gerolymatos S.A. continues to attempt to further develop and capitalize on said program. Defendants further admit that Gerolymatos S.A. and the Danish pharmaceutical company, H. Lundbeck entered into a license agreement for, *inter alia*, the marketing of clioquinol for Alzheimer's Disease. Defendants admit that, although substantially hindered by the actions of Prana as alleged in the Second, Third and Fourth Counterclaims of this pleading, the '852 and '323 patents and/or the applications on which those patents issued and corresponding international patents and applications did further Gerolymatos S.A.'s ability to develop and fund said program. Finally, Defendants admit that no proceeds of the agreement between H. Lundbeck and Gerolymatos S.A. were shared with Plaintiffs. Defendants deny all of the remaining allegations of paragraph 23 of the Complaint, including any implicit allegation that "the use of clioquinol in Alzheimer's Disease" was Plaintiffs' invention, and any implicit allegation that Plaintiffs were or are entitled to a share of any proceeds of said program.

24. Defendants lack sufficient information to form a belief as to the truth of the allegations of paragraph 24 of the Complaint and therefore deny same.

25. Defendants repeat and reallege the allegations, admissions and denials of paragraphs 1-24 of this Answer as if herein set forth in full.

26. Defendants deny the allegations of paragraph 26 of the Complaint.

27. Defendants admit that Bush, Cherny and Tanzi were not named as inventors on the '852 and '323 patents. Defendants deny all of the remaining allegations of paragraph 27 of the Complaint, including any implicit allegation that Bush, Cherny and Tanzi should have been named as inventors on such patents.

28. Defendants admit the allegations of paragraph 28 of the Complaint.

29. Defendants deny the allegations of paragraph 29 of the Complaint.

30. Defendants deny the allegations of paragraph 30 of the Complaint.

31. Defendants repeat and reallege the allegations, admissions and denials of paragraphs 1-30 of this Answer as if herein set forth in full.

32. Defendants deny the allegations of paragraph 32 of the Complaint.

33. Defendants deny the allegations of paragraph 33 of the Complaint.

34. Defendants repeat and reallege the allegations, admissions and denials of paragraphs 1-33 of this Answer as if herein set forth in full.

35. Defendants deny the allegations of paragraph 35 of the Complaint.

36. Defendants deny the allegations of paragraph 36 of the Complaint.

37. Defendants repeat and reallege the allegations, admissions and denials of paragraphs 1-36 of this Answer as if herein set forth in full.

38. Defendants deny the allegations of paragraph 38 of the Complaint.

39. Defendants deny the allegations of paragraph 39 of the Complaint.

40. Defendants deny the allegations of paragraph 40 of the Complaint.

AFFIRMATIVE DEFENSES

Defendants, in further answer to the Complaint and as separate, affirmative defenses thereto, allege the following:

41. This Court lack jurisdiction over the person of Gerolymatos.

42. Gerolymatos is the inventor of the inventions claimed in the '852 and '323 patents.

43. None of Bush, Cherny and Tanzi are inventors of the inventions claimed in the '852 and '323 patents.

44. By virtue of affirmative representations made by Plaintiffs and relied upon by Defendants to their material prejudice and detriment, Plaintiffs are estopped from asserting that Bush, Cherny or Tanzi is an inventor of the inventions claimed in the '852 and '323 patents or that MGH or Prana has any right or interest in said patents.

45. Counts III and IV of the Complaint are barred by statute of limitations.

COUNTERCLAIMS BY GEROLYMATOS S.A.

Defendant, Gerolymatos S.A. states the following counterclaim against Plaintiffs:

FIRST COUNTERCLAIM: DECLARATORY JUDGMENT

46. This is a claim for declaratory relief under 28 U.S.C. § 2201. This Court has jurisdiction over the subject matter of this claim pursuant to 28 U.S.C. §§ 1331 and 1338(a).

47. Gerolymatos S.A. repeats and realleges the allegations of paragraphs 1- 45 of this pleading as if here set forth in full.

48. By virtue of *inter alia*, the allegations of the Complaint in this Action and the allegations of this Answer, there is a justiciable controversy between Plaintiffs and Gerolymatos S.A. as to whether Bush, Cherny and Tanzi are inventors of the '852 and '323 patents and whether MGH and the Prana are assignees of said patents.

49. Gerolymatos S.A. is entitled to a declaratory judgment that Bush, Cherny and Tanzi are not inventors of the '852 and '323 patents, and that MGH and Prana are therefore not assignees of said patents.

Defendant, Gerolymatos S.A. states the following additional counterclaims against Prana:

**SECOND COUNTERCLAIM – TORTIOUS INTERFERENCE
WITH CONTRACTUAL RELATIONS**

50. This is a claim for tortious interference with contractual relations. This Court has jurisdiction over the subject matter of this claim pursuant to 28 U.S.C. §§1338(b) and 1367(a).

51. Gerolymatos S.A. repeats and realleges the allegations of paragraphs 1 - 49 of this pleading as if here set forth in full.

52. Gerolymatos S.A. entered into contractual relations with H. Lundbeck A.S. (hereinafter "Lundbeck") which included, among other things, licenses to the patent applications which issued as the '852 and '323 patents.

53. With knowledge of the contractual relations stated in paragraph 52, Prana's directors, officers, employees and/or agents made false and misleading representations to Lundbeck regarding rights or interests in and inventorship of the subject matter of the '852 and '323 patents.

54. Upon information and belief, the false and misleading representations referred to in paragraph 53 were made with the intent of interfering with the contractual relationship between Gerolymatos S.A. and Lundbeck.

55. The false and misleading representations referred to in paragraph 53 interfered with and disrupted the contractual relationships between Gerolymatos S.A. and Lundbeck, thereby causing substantial damage to Gerolymatos S.A.

THIRD COUNTERCLAIM – UNFAIR COMPETITION IN
VIOLATION OF § 43(A) OF THE LANHAM ACT

56. This is a claim for violation of § 43(a) of the Lanham Act, 15 U.S.C. § 1125(a). This Court has jurisdiction over the subject matter of this claim pursuant to 28 U.S.C. § 1331.

57. Gerolymatos S.A. repeats and realleges the allegations of paragraphs 1- 55 of this pleading as if here set forth in full.

58. Subsequent to commencement of this Action, Prana issued a press release in which it made false and misleading representations regarding Gerolymatos S.A.

59. By virtue of its representations referred to in paragraphs 53 and 58 of this pleading, Prana, in connection with its goods or services relating to clioquinol for the treatment of Alzheimer's Disease, has used in commerce false and misleading descriptions and representations of fact, which in advertising or promotion, misrepresent the nature, characteristics or qualities of Gerolymatos S.A.'s goods, services and/or commercial activities.

60. Gerolymatos S.A. has been and is likely to be substantially damaged by Prana's acts alleged in paragraph 59.

**FOURTH COUNTERCLAIM - TORTIOUS INTERFERENCE
WITH PROSPECTIVE BUSINESS RELATIONS**

61. This is a claim for tortious interference with prospective business relations. This Court has jurisdiction over the subject matter of this claim pursuant to 28 U.S.C. §§ 1338(b) and 1367(a).

62. Gerolymatos S.A. repeats and realleges the allegations of paragraphs 1 - 60 of this pleading as if here set forth in full.

63. The false and misleading representations referred to in paragraph 53 and 58 have interfered with prospective business relationships of Gerolymatos S.A., thereby causing substantial damage to Gerolymatos S.A.

WHEREFORE, Defendants request that this Court:

A. Issue a declaration adjudging that Ashley L. Bush, Robert Cherny and Rudolph E. Tanzi are not inventors of United Patent Nos. 6,001,852 and 5,994,323 and that The General Hospital Corporation, doing business as Massachusetts General Hospital, and Prana Biotechnology, Ltd., are not assignees of said patents;

B. Preliminarily and permanently enjoin Plaintiffs, their directors, officers, employees, agents and all persons in active concert or participation with them, from stating or representing that Ashley L. Bush, Robert Cherny and/or Rudolph E. Tanzi are inventors of United Patent Nos. 6,001,852 and 5,994,323, or that The General Hospital Corporation and/or Prana Biotechnology, Ltd. are assignees of said patents; and

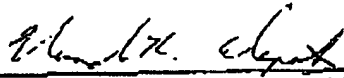
C. Award P.N. Gerolymatos S.A. compensatory damages;

D. Award P.N. Gerolymatos S.A. its costs incurred in prosecuting this Action, including reasonable attorneys' fees; and

E. Award P.N. Gerolymatos S.A. such other and further relief as this Court deems just and proper.

Dated: December 7, 2001

By:


Paul Zegger (D.C. Bar No. 457,399)
Nanda K. Alapati (D.C. Bar No. 450,142)

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(202) 496-4400

Attorneys for Defendants
P.N. GEROLYMATOS S.A. and
PANAYOTIS N. GEROLYMATOS

Of Counsel:

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New York, NY 10036
(212) 790-9090

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that the foregoing Amended Answer and Counterclaims,
was served this 7th day of December, 2001, via Federal Express, to the following.

William G. McElwain, Esq.
Hale and Dorr LLP
1455 Pennsylvania Avenue, N.W.
Washington, D.C. 20004

William F. Lee, Esq.
Hale and Dorr LLP
60 State Street
Boston, Massachusetts 02109

Handwritten signature